**STATE BOARD OF OPTOMETRY**
2450 DEL PASO ROAD, SUITE 105, SACRAMENTO, CA 95834
P (916) 575-7170 F (916) 575-7292 www.optometry .ca.gov

# Continuing Education Course Approval Checklist

Title: Retinal and Choroidal Dystrophies

Provider Name: Dr. Jennifer Kim

☑Completed Application
Open to all Optometrists? ☑Yes ☐No
Maintain Record Agreement? ☑Yes ☐No

☑Correct Application Fee

☑Detailed Course Summary

☑Detailed Course Outline

☑PowerPoint and/or other Presentation Materials

☐Advertising (optional)

☑CV for EACH Course Instructor

☑License Verification for Each Course Instructor
Disciplinary History? ☐Yes ☑No

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| Cashiering and Board Use Only | | | |
|---|---|---|---|
| Receipt # | Payor ID | Beneficiary ID | Amount |
| 1-2769 | 3815685 | 1450694 | 50 |

# CONTINUING EDUCATION COURSE APPROVAL APPLICATION

**$50 Mandatory Fee**

Pursuant to California Code of Regulations (CCR) § 1536, the Board will approve continuing education (CE) courses after receiving the applicable fee, the requested information below and it has been determined that the course meets criteria specified in CCR § 1536(g).

In addition to the information requested below, please attach a copy of the course schedule, a detailed course outline and presentation materials (e.g., PowerPoint presentation). Applications must be submitted 45 days prior to the course presentation date.

**Please type or print clearly.**

| **Course Title** | **Course Presentation Date** |
|---|---|
| RETINAL AND CHOROIDAL DYSTROPHIES | 03/14/2017 |

**Course Provider Contact Information**

**Provider Name**

JEONG-AH (First) KIM (Last) JENNIFER (Middle)

**Provider Mailing Address**

27107 TOURNEY RD

**Street** **City** SANTA CLARITA **State** CA **Zip** 91355

**Provider Email Address** jenniferkim100@hotmail.com

| | |
|---|---|
| **Will the proposed course be open to all California licensed optometrists?** | ☒ YES ☐ NO |
| **Do you agree to maintain and furnish to the Board and/or attending licensee such records of course content and attendance as the Board requires, for a period of at least three years from the date of course presentation?** | ☒ YES ☐ NO |

**Course Instructor Information**

Please provide the information below and attach the curriculum vitae for each instructor or lecturer involved in the course. If there are more instructors in the course, please provide the requested information on a separate sheet of paper.

**Instructor Name**

HOWARD (First) COHEN (Last) (Middle)

| | |
|---|---|
| **License Number** 2009-00411 (North Carolina) | **License Type** MD |
| **Phone Number** ( ) | **Email Address** hcohen33@gmail.com |

***I declare under penalty of perjury under the laws of the State of California that all the information submitted on this form and on any accompanying attachments submitted is true and correct.***

*Signature of Course Provider* *Date* 2-1-17

27107 Tourney Road

Santa Clarita, CA 91355

February 9, 2017

CALIFORNIA BOARD OF OPTOMETRY
2450 Del Paso Road, Suite 105

Sacramento, CA 95834

To whom it may concern:

I am submitting a request for continuing education approval for the Kaiser Permanente Mammoth Ocular Symposium (3/12/17-3/14/17) less than the required 45 days because we have had a last minute cancellation from one of our speakers. Thus, Drs. Howard Cohen and Gary Groesbeck have volunteered to give lectures to replace the speaker who had to cancel.

Thank you so much for your understanding and my apologies for this unforeseeable change in our speakers.

If you need to contact me, please email me at jenniferkim100@hotmail.com or call me at 323-574-8957.

Sincerely,

Jeong-Ah Jennifer Kim, OD
CA Lic 11674TLG

27107 Tourney Road
Santa Clarita, CA 91355
March 4, 2017

State Board of Optometry
2450 Del Paso Road, Suite 105
Sacramento, CA 95834

To whom it may concern:

Thank you for your attention to the Kaiser Permanente Mammoth Ocular Symposium 2017 continuing education approval submission. In anticipation of receiving deficiency notifications for the other lectures, I have included a summary of each of the lectures and the respective powerpoint presentations.

There will be 7 lectures from 3/12/17-3/14/17:

The Retinal and Choroidal Dystrophies lecture is relevant to diagnosing and providing proper care as optometrists perform retinal exams on a regular basis. As optometrists continue to go toward medical aspects of eye care, this lecture will keep us well informed regarding various retinal conditions.

The Update on Cataract Surgery is relevant to optometrists because this is one of the most common referrals we make. It is important for optometrists to remain informed about advancements and changes to cataract surgeries so that we can properly educate our patients.

The Retinal White Dot Syndromes lecture is relevant in providing proper optometric care with respect to retinal diseases. Such retinal conditions may lead to discovering the underlying systemic condition giving rise to the specific white dot syndrome.

The Corneal Ectasias and Cross-Linking lecture provides information for conditions such as keratoconus and its treatment with cross-linking. Optometrists are often the first to diagnose keratoconus thus it's important that we know about various medical treatments, in addition to contact lenses and glasses.

The IOL Materials and Design lecture provides information regarding the details of lens implants for cataract patients. IOL materials and designs are topics that are commonly discussed between optometrists and their patients.

The Sports Injuries lecture is relevant as patients come into our clinics with various sports injuries sustained at school, sporting teams/clubs, and times of recreation. It is

important to anticipate and know what injuries can be sustained as optometrists provide a wide range of eye care.

The Benign Eyelid Lesions lecture provides information and visuals regarding eyelid lesions that optometrists observe daily. This will help to properly diagnose benign lesions and contrast those with lesions that need further work ups and/or referrals.

I apologize for submitting the lectures less than the 45 day request. I was waiting for all the presentations so that the lectures can be submitted together. The Benign Eyelid Lesions and Sports Injuries lectures were submitted less than the 45 request because there was a last minute cancellation of one of the original speakers, thus Drs. Groesbeck and Cohen prepared the presentations thereafter. In the future, an earlier deadline will be proposed so that the submissions will be on time.

I am attaching 2 checks that have already been deposited, one for $250 and the other for $100. All the files could not be sent in one email because the files were too large so there are 3 emails total which contain the required documents.

Thank you very much for your attention.

Sincerely,

Jeong-Ah Jennifer Kim, OD
CA Lic 11674TLG

RETINAL AND CHOROIDAL
DYSTROPHIES

HOWARD B. COHEN MD

IMPACT OF CHILDHOOD BLINDNESS

GLOBALLY THE INCIDENCE OF CHILDHOOD BLINDNESS IS 1 PER 1000

IN 2014 THERE WERE 1.5 MILLION BLIND CHILDREN WORLDWIDE

THIS EQUATES TO 75 MILLION PERSON YEARS OF BLINDNESS

IMPACT OF CHILHOOD BLINDNESS

COMBINED CATAGORIES OF LOW VISION ARE 3 - 10 TIMES

MORE COMMON THEN BLINDNESS

COST ESTIMATES 6 - 27 BILLION DOLLARS

IMPACT OF CHILDOOD VISUAL IMPAIRMENT USA

1% OF PERSONS UNDER 18 HAD VISUAL IMPAIRMENT NOT CORRECTED BY GLASSES

VISUAL DISABLED AGES 4-20 = 665,200

INFORMAL CARE PRODUCTIVITY LOSS FOR AGES 0-17 = $601,868,206

VISUAL IMPAIRMENT

STUDENTS WITH VISUAL IMPAIRMENT MORE LIKELY THEN OTHER STUDENTS WITH DISABLITIES TO GET A AVERAGES

ONLY 29% OF VISUALLY IMPAIRED STUDENTS ARE EMPLOYED 3 - 5 YRS AFTER SECONDARY SCHOOL

NORMAL RETINA

NORMAL RETINA

VISUAL CYCLE

VISUAL CYCLE

NORMAL RETINA

INHERITANCE PATTERNS

INHERITANCE PATTERNS

INHERITANCE PATTERNS

RETINITIS PIGMENTOSA
INCIDENCE

HIGH - 5 / 1000

LOW - 1 / 7000

REPRESENTS DIFFERENCES IN DISTRIBUTION AND ACCURACY OF SAMPLE

MALES 55-60 %

OCCURS IN ALL RACES

HEREDITARY PATTERNS

FREQUENCY DEPENDS ON THE METHOD USED TO COLLECT THE DATA

ALTHOUGH SPORADIC OR ISOLATED TYPES ARE MOST COMMON MANY OF THESE ARE THOUGHT TO BE RECESSIVE

HEREDITARY PATTERNS

RECESSIVE IS MOST COMMON WHEN ISOLATED CASES ARE INCLUDED

DOMINANT FOLLOWS WITH 9 TO 20%

X - LINKED 4 - 20%

RETINITIS PIGMENTOSA CLASSIC TRIAD

ATTENUATION OF VESSELS

RETINAL PIGMENTARY CHANGES

PALLOR OF THE OPTIC NERVE

RETINITIS PIGMENTOSA

ATTENUATION OF VESSELS

DEATH OF THE RODS LEADS TO LOSS OF CELL MASS IN THE NUCLEAR LAYERS AND DEGENERATION OF ASSOCIATED NEURONS

THESE CHANGES ALLOW INCREASED OXYGEN TO REACH THE INNER RETINA

ATTENUATION OF VESSELS

INCREASED OXYGEN IN THE INNER RETINA LEADS TO THE ATTENUATION OF VESSELS OBSERVED IN RP

PIGMENTARY CHANGES

BONE SPICULES COMMON BUT NOT REQUIRED FOR THE DIAGNOSIS

ANIMAL STUDIES SHOW THAT BONE SPICULES DEVELOP WHEN THE RETINAL VESSELS TOUCH THE RPE

PIGMENTARY CHANGES

THE AMOUNT AND SHAPE REFLECT THE RETINAL VESSELS IN THE AREA AT THE TIME.

RPE CELL FORM AROUND THE VESSELS TO ESTABLISH AN NEW BLOOD RETINAL BARRIER

NORMAL RETINA

RETINITIS PIGMENTOSA
BONE SPICULES

RETINITIS PIGMENTOSA
BONE SPICULES

RETINITIS PIGMENTOSA

RETINITIS PIGMENTOSA

OPTIC NERVE CHANGES

CHANGES PARALLEL THE DEGREE OF LOSS OF PHOTORECEPTORS

LATE THE DISC WILL HAVE A HARD , YELLOW , WAXY APPEARANCE DENOTING SECONDARY OPTIC ATROPHY

RETINITIS PIGMENTOSA

MACULAR CHANGES IN RETINITIS PIGMENTOSA

ATROPHIC MOST COMMON IN PATIENTS WITH LESS THEN 20 / 200

ATROPHY RESULTS FROM RPE DEGENERATION RESULTING FROM CME OR CONE LOSS

MACULAR CHANGES IN RETINITIS PIGMENTOSA

ROD DEGENERATON LEADS TO NUTRITIONAL DEFICIENCES AND CONE DEATH DRIVEN BY THE INSULIN/MTOR PATHWAY

MAMMALIAN TARGET OF RAPAMYCIN PATHWAY

MACULAR CHANGES IN RETINITIS PIGMENTOSA

SOME INVESTIGATORS BELIEVE THAT RODS PRODUCE A CONE PROTECTIVE FACTOR AND LOSS OF RODS AND THIS FACTOR RESULTS IN LOSS OF CONES

MACULAR CHANGES IN RETINITIS PIGMENTOSA

INVESTIGATORS FROM JOHNS HOPKINS FOUND THAT CONES DIE FROM OXIDATIVE DAMAGE.

ANTIOXIDANTS IMPROVED CONE FUNCTION AND DENSITY

RETINITIS PIGMENTOSA

MACULAR CHANGES IN RETINITIS PIGMENTOSA

CME IN RP

CME PRESENT IN 13 - 70%

25% HAVE 20/25 OR BETTER VA

WIDTH OF TOTAL AREA OF CYSTOID CHANGES IS SIGNIFICANTLY CORRELATED WITH VISION

CME IN RP

BREAKDOWN OF BRB

FAILURE OF PUMPING OF RPE CELLS

MULLER CELL DYSFUNCTION

ANTI RETINAL ANTIBODIES

VITREOUS TRACTION

MISC

CME IN RP

OCT IS DIAGNOSTIC MODALITY OF CHOICE

CME MAY RESULT FROM LEAKAGE FROM PERIFOVEAL CAPILLARIES OR FROM MORE PERMEABLE RPE

CME IN RP

HAJANI BJO 2008 STUDIED PREVALENCE OF CME IN RP

124 PATIENTS WITH RP. 38% UNILATERAL AND 27% OU WITH CME

AD - 52%, AR 39%,ISOLATED 39%, USHER'S 35%,XLINKED 0

CME IN RP

HAJANI, EYE 2009 FOUND THAT OCT CAN REVEAL CME WHEN OPHTHALMOSCOPY OR CTL DID NOT.

50 PATIENTS . 20(32%)UNILATERAL AND 11 (18%) OU HAD CME ON OCT

RETINITIS PIGMENTOSA

RETINITIS PIGMENTOSA

MACULAR CHANGES IN RETINITIS PIGMENTOSA

MACULAR CHANGES IN RETINITIS PIGMENTOSA

MANY CASES OF ATROPHIC MACULAR ARE RESULT OF LONG STANDING CME

OPHTHALMIC SURGERY 2010. PATIENTS WITH 20/200 OR WORSE .19% CME , 81% ATROPHIC

RETINITIS PIGMENTOSA

RETINITIS PIGMENTOSA

MACULAR CHANGES IN RETINITIS PIGMENTOSA

EPIRETINAL MEMBRANE NOT UNCOMMON

SRNV

RETINITIS PIGMENTOSA

ASSOCIATED FINDINGS

VITREOUS OPACITIES - PRUETT EXAMINED 116 PATIENTS WITH RP AND ALL HAD OPACITIES.

OPACITIES INCREASE WITH AGE AND HAVE NO AFFECT ON VISION

RETINITIS PIGMENTOSA

ASSOCIATED FINDINGS

PSC FOUND IN 11 - 20%

PRESENT IN 60% OF RP PATIENTS OVER 40

INCREASED INCIDENCE OF MYOPIA

X LINKED CARRIERS

X - LINKED CARRIER (FEMALES) MAY HAVE VARIABLE CHANGES IN THE RPE. ALL FEMALES IN AN RP FAMILY SHOULD HAVE A DILATED , CAREFUL FUNDUS EXAM.

X LINKED CARRIER

X LINKED CARRIER

X LINKED CARRIERS

ERG ABNORMAL IN 54 - 96%

EOG ABNORMALITY ALONE IN 6.5%

OCT SHOWS INCREASED REFLECTIVITY FROM RPE

SINE PIGMENTO

PIGMENT CHANGES ARE OFTEN VERY SUBTLE.

FA WILL OFTEN REVEAL SOME PIGMENT CHANGES

MAY BE EARLY FORM OF DISEASE AS INCIDENCE IS HIGHER WITHIN FIRST 3YRS OF DIAGNOSIS

SINE PIGMENTO

UNILATERAL

MUST HAVE EXTINGQUISHED ERG IN AFFECTED EYE AND NORMAL IN OTHER EYE

MOST ARE ISOLATED CASES

OFTEN PROGRESSES TO BILATERAL

UNILATERAL

MUST BE FOLLOWED FOR 5 YEARS BEFORE MAKING THE DIAGNOSIS

100 VALID CASES REPORTED

INVERSE

VERY UNCOMMON AND MAY BE MISDIAGNOSED CONE DYSTROPHY

SECTOR

DOMINANT OR RECESSIVE

INFERIOR QUADRANTS IN 50%

INFERIOR NASAL NEXT MOST COMMON

USUALLY SYMMETRICAL

DARK ADAPTATION MAY BE NORMAL

SECTOR

IF BOTH NASAL QUADRANTS ARE INVOLVED A BITEMORAL FIELD DEFECT IS PRESENT

ERG SUBNORMAL

CAN BE ASYMPTOMATIC UNTIL 5 - 6TH DECADE

DEAFNESS IN MANY CASES

RETINITIS PIGMENTOSA

RETINITIS PIGMENTOSA

DIFFERENTIAL

CONGENITAL AND ACQUIRED SYPHILIS

RUBELLA

OTHER VIRAL

TRAUMA

DRUGS

SYPHILIS

RUBELLA

MELLARIL

DIFFERENTIAL

OTHER RETINAL AND CHOROIDAL DYSTROPHIES

PIGMENTED PARAVENOUS ATROPHY

DIAGNOSTIC TESTS

COLOR VISION - PARALLELS CONE HEALTH. BLUE - YELLOW MOST COMMON

FA - CME AND DEGREE OF ATROPHY

OCT - CME AND RETINAL THICKNESS AS WELL AS RETINAL ANATOMY WITH SDOCT

OCT

OCT

OCT IN RETINITIS PIGMENTOSA

DIAGNOSTIC TESTS

DARK ADAPTATION - EARLIEST DEFECT EXCEPT FOR ERG

NOT ALWAYS AVAILABLE. I ALWAYS USED A SIMPLE TEST THAT YOU CAN DO IN YOUR OFFICE AND TAKES ONLY A FEW MINUTES ... UNLESS YOU HAVE RP

DIAGNOSTIC TESTS - ERG

ERG ABNORMALITY IS REQUIRED TO MAKE THE DIAGNOSIS

WILL BE ABNORMAL LONG BEFORE CLINICAL SYMPTOMS OR FINDINGS OCCUR

ERG IN RP

ERG FINDING IS RP

DECREASED AMPLITUDE OF SCOTOPIC B WAVE

IMPLICIT AND LATENT TIMES VARY IN FAMILIES

PHOTOPIC NORMAL IN EARLY CASES. ABNORMAL LATE

ERG FINDINGS IN RP

TWO TYPES OF ERG; SINGLE FLASH AND MULTI FOCAL

CONVENTIONAL ERG IS A MASS RESPONSE. FOCAL ERG WILL MEASURE AT SET DEGREES

ERG FINDINGS IN RP

MULTI FOCAL ERG CAN PROVIDE A HIGH RESOLUTION MAPPING OF THE POSTERIOR POLE

IN MULTIFOCAL ERG IMPLICIT TIME IS MORE MORE SENSITIVE A PREDICTOR THEN AMPLITUDE

MULTI FOCAL ERG

MULTI FOCAL ERG

MULTI FOCAL ERG

EOG

NOT AS RELIABLE IN RETINITIS PIGMENTOSA AS THE ERG

USEFUL IN DIAGNOSING THE CARRIER STATE OF X LINKED RETINITIS PIGMENTOSA

VISUAL FIELD DEFECTS

MOST COMMON IS RING OR ANNULAR FIELD LOSS

WILL VARY DEPENDING ON TYPE OF RP AND HEREDITARY PATTERN

USUALLY START IN INFERIOR TEMPORAL QUADRANT

VISUAL FIELD DEFECT

RING SCOTOMA USUALLY BETWEEN THE 10 - 40 MERIDIAN. CAN HAVE DOUBLE RING WHICH JOIN OVER TIME

ADVANCED CASES 5 - 10 DEGREES " GUN BARREL"AND SMALL ISLAND INFRO TEMP

VISUAL FIELD IN RP

VISUAL FIELD IN RP

DNA TESTING

29 laboratories in the United States. 6 in California.

30 laboratories world wide.

In addition there are numerous research centers that perform DNA testing.

DNA TESTING

293 retinal diseases have been mapped.

256 identified at DNA level

Total number of gene loci dominant RP 23 Identified genes 22. Recessive 39 loci 36 genes.

DNA TESTING

X Linked RP 5 gene loci. 1 gene.

Leber Congenital Amaurosis autosomal dominant 1 gene loci. 1 gene. Recessive 12 gene loci. 12 genes.

CLINICAL COURSE

ONSET USUALLY IN TEENS BUT ERG FINDINGS ARE PRESENT MUCH EARLIER THEN SYMPTOMS OF CLINICAL CHANGES.

CLINICAL COURSE

FIRST SYMPTOM IS OFTEN NYCTALOPIA OR FIELD DEFECT

IN SOME CASES DIAGNOSIS NOT MADE UNTIL CATARACT, MACULAR , OR CONE INVOLVEMENT

CLINICAL COURSE

PROGRESSION DEPENDS ON MODE OF TRANSMISSION

DOMINANT MOST BENIGN WITH VA 20/30 - 100 UNTIL 5TH AND 6TH DECADE

RECESSIVE, ISOLATED AND X - LINKED MOST SEVERE

CLINICAL COURSE

FISHMAN REPORTED THAT ALL HIS X - LINKED OVER 30 HAD 20/80 OR LESS. RECESSIVE HAD SIMILIAR RESULTS

TOTAL BLINDNESS IN THESE MODES COMMON BUT SOME DO RETAIN VA INTO SIXTIES

CLINICAL COURSE

CHECK THE FAMILY. THAT WILL OFTEN TELL MORE ABOUT THE PROGESSION FOR A PARTICULAR INDIVIDUAL

GOOD FAMILY HISTORY IMPORTANT. PATIENTS HAVE TO MAKE THE CALL TO RELATIVES

Treatment

VITAMIN A SUPPLEMENTATION

DOCOSAHEXAENOIC ACID – DHA

LUTEIN

GANGLIOSIDES

BETA-CAROTENE ACID

ORAL VALPROIC ACID

CILIARY NEUROTROPHIC FACTOR-CNTF

HYPERBARIC OXYGEN

TREATMENT

IN 1993 BERSON ET AL REPORTED THAT TREATMENT WITH 15000 IU OF VITAMIN A PALMINTATE SLOWED THE PROGRESSON OF CONE ERG

TREATMENT

NEI CONFIRMED VALUE OF VITAMIN A IN RP BUT CAUTIONED USE IN OTHER HEREDITARY DISEASES AS IT CAUSES ACCELERATED INCREASE IN LIPOFUCSIN.

FISH OIL HAS SHOWN BENEFIT. AFFECTS RATE OF DECLINE OF ERG AMPLITUDES.

TREATMENT OF CME IN
RETINITIS PIGMENTOSA

CARBONIC ANHYDRASE INHIBITORS

DIAMOX

METHAZOLAMIDE

DORZOLAMIDE

TREATMENT OF CME IN RETINITIS PIGMENTOSA

DIAMOX HAS BEEN SHOWN IN SEVERAL STUDIES TO BE EFFECTIVE IN REDUCING MACULAR EDEMA AND RETINAL THICKNESS. VISUAL RESULTS ARE VARIABLE .

TREATMENT OF CME

SIDE EFFECTS ARE COMMON AND REBOUND OCCURS IN OVER 30%

METHAZOLMIDE NOT AS EFFECTIVE

DORZOLAMIDE DROPS

TREATMENT OF CME

DORZOLAMIDE DROPS REDUCES THICKNESS WITH VARIABLE VA RESULTS. REBOUND IN 31%

STUDIES COMPARING DROPS TO ORAL INDICATE ORAL MORE EFFECTIVE

TREATMENT OF CME

INTRAVITREAL KENALOG HAS HAD BETTER ANATOMIC THEN VISUAL RESULTS. SEVERAL RISK FACTORS

IVK CAN BE USED IN COMBINATION THERAPY

TREATMENT OF CME WITH ANTI VEGF

ONLY A FEW REPORTED STUDIES AND CASE REPORTS

30 PATIENTS WITH 6 MONTH HISTORY OF CME FAILED ON DIAMOX. 15 INJECTED WITH 0.5 LUCENTIS. 87% SIGNIFICANT RESOLUTION OF CME AT 6 MONTHS ON SINGLE INJECTION. NO DIFFERENCE IN VISION.

RETINITIS PIGMENTOSA

TREATMENT OF CME WITH ANTI VEGF

AVASTIN 1.25 MG IN 13 EYES OF 7 PATIENTS. WAS FOUND TO BE EFFECTIVE IN REDUCING THICKNESS AND IMPROVING VISUAL ACUITY

2 CASES BOTH FAILED WITH AVASTIN BUT RESPONDED TO IVK

TREATMENT OF CME WITH ANTI VEGF

TWO REPORTS OF TREATMENT OF CME SECONDARY TO RP WITH AFIBERCEPT ( EYLEA).

MOUSTAFA BMC 2015- SINGLE INJECTION OF 0.05ML/0.50MG EYLEA.IMPROVED VISION AND DECREASED THICKNESS LASTED AT 3 AND 6 MONTH EXAMS.

TREATMENT OF CME WITH ANTI VEGF

NORMAL RETINA

NORMAL RETINA

ON THE HORIZON

CELLS TAKEN FROM DEVELOPING RETINAS AT THE TIME OF PEAK ROD GENESIS WILL RESULT IN SYNAPTIC CONNECTIONS,INTEGRATION AND IMPROVEMENT OF VISUAL ACUITY

ON THE HORIZON

OTANI, ET AL J.CLIN. INVEST 2004 DEMOSTRATED THAT INJECTION OF BONE MARROW DERIVED HEMATOPOIETIC STEM CELLS INTO THE VITREOUS PREVENT CONE LOSS

ON THE HORIZON

THE STEM CELLS CONTAIN ENDOTHELIAL PRECURSORS WHICH INCORPORATE INTO VESSELS THAT WOULD DISAPPEAR SECONDARY TO ROD DEATH

USING AUTOLOGOUS CELLS PREVENTS REJECTION

ON THE HORIZON

GENE THERAPY. 2010 SUN ET AL. REPORTED THAT THEY WERE ABLE TO ACHIEVE RESCUE OF BOTH ROD AND CONES WITH A SINGLE PROMOTER. THIS WAS A FIRST AND CAN LEAD TO HUMAN TRIALS.

ARGUS II RETINAL PROSTHESIS

ARGUS II RETINAL PROSTHESIS

PROGNOSIS

VARIES SIGNIFICANTLY AMONG INHERITANCE TYPES

SANDBERG IO 2008 FOUND THAT RECESSIVE ( USH2A)MEAN ANNUAL DECLINE VA 2.6%, VF 7%,ERG13.2%

FASTER THEN DOM (RHO), SLOWER THEN X-LINKED (RPGR)

PROGNOSIS

BERSON EER 2007 STUDIED HOW LONG FOR CONE ERGS TO CHANGE FROM 30HZ TO 0.05MIRCO V ( VIRTUAL BLINDENESS).

10% OF CONE ERG PER YEAR NOT ON RX, 8.3% ON RX

PROGNOSIS

BERSON - IF PATIENT HAS A 3.5 MICRO V AT AGE 40 (25% OF RP PATIENTS) PATIENT WOULD BE EXPECTED TO RETAIN SOME USEFUL VA FOR THEIR ENTIRE LIFE WITHOUT RX

PROGNOSIS

BERSON INVES OPHTH 2002 STUDIED THE PROGRESSION IN THE DOMINANT FORM OF RP WITH RHODOPSIN MUTATIONS

20 - 25 % OF DOMINANT HAVE THESE MUTATIONS

100 DIFFERENT MUTATIONS PRESENT

PROGNOSIS

3 MAIN TYPES OF RHODOPSIN MUTATIONS FOUND

GLOBULE 39% , PLUG 14%, AND C-TERMINAL 20%

RATE OF VA LOSS DID NOT VARY AMONG GROUPS

PROGNOSIS

FIELD LOSS AND ERG DECLINE WAS GREATEST FOR C-TERMINAL AND LEAST FOR PLUG

MEAN ANNUAL DECLINE WAS 1.86% VA, 2.65% VF, 8.7% ERG

SYNDROMES

DEAFNESS MAY OCCUR IN UP TO 40% OF ALL CASES OF RP

THIS IS BELIEVED TO BE BASED ON SIMILAR EMBRYOLOGICAL ORIGIN OF THE RPE AND THE EPITHELIUM OF THE ORGAN OF CORTI

USHER'S SYNDROME

LEADING CAUSE OF DEAFNESS AND BLINDNESS WORLDWIDE

20,000 CASES IN US

3 - 6% OF ALL DEAF AND HARD OF HEARING CHILDREN

USHER'S SYNDROME

9 GENES ISOLATED

3 TYPES OF USHER'S

95% ARE TYPES 1 AND 2

AUTOSOMAL RECESSIVE

USHER'S SYNDROME

TYPE 1 - PROFOUND HEARING LOSS , RP , BALANCE PROBLEMS. 5 GENES

TYPE 2 - MOD - SEVERE HEARING LOSS , RP , NO BALANCE PROBLEMS.3 GENES

TYPE 3 - PROGRESSIVE HEARING LOSS,RP , + - . 1 GENE

OTHER SYNDROMES

HALLGREN'S

REFSUM'S

COCKAYNE'S

ALSTROM'S

DIALINAS - AMALRIC

LAWRENCE-MOON-BARDET-BIEDL

LEBER'S CONGENITAL AMAUROSIS ( LCA)

LCA IS NOT UNCOMMON. 2 -3 / 100,000. 18% OF CONGENITALLY BLIND IN HOLLAND, 10% IN SWEDEN

AUTOSOMAL RECESSIVE.

LCA

DECREASED VISION AT BIRTH OR WITHIN FIRST YEAR

NYSTAGMUS COMMON

PHOTOPHOBIA

MINIMALLY REACTIVE PUPILS

VARIABLE PIGMENTARY CHANGES IN RETINA,OPTIC PALLOR,VESSEL ATTENUATION

LCA

LCA

LCA

NOBLE AND CARR REPORTED THAT 95% OF THEIR PATIENTS HAD VA OF 20/200 OR LESS WITH THE MAJORITY HM TO CF

GENE THERAPY FOR LCA

1997 - NEI INVESTIGATION FOUND THAT MUTATION IN RPE65 GENE CAUSED LCA TYPE OF VISUAL LOSS IN DOGS

2000 - DOGS WERE INJECTED WITH SINGLE DOSE OF GENE TRANSFER THERAPY

GENE THERAPY FOR LCA

INJECTION CONSISTED OF COPIES OF RPE65

DOGS HAD SIGNIFICANT IMPROVEMENT OF VA AND NYSTAGMUS WAS CORRECTED

AAV

LACK OF PATHOGENICITY

MIMIMAL IMMUNOGENICITY

MAINTAIN HIGH LEVELS OF TRANGENE EXPRESSION IN RPE , PHOTORECEPTORS , GANGLION CELLS FOR LONG PERIODS WITH A SINGLE INJECTION

GENE THERAPY FOR LCA

GENE THERAPY FOR LCA

GENE THERAPY FOR LCA

PHASE 1 CLINICAL TRIAL IN 2008. 3 PATIENTS AGES 22,24, 25 INJECTED SUBRETINALLY WITH AAV-RPE65.

OVER 90 DAYS THERE WAS A 50 FOLD INCREASE IN DAY VA AND 63000 FOLD IN NIGHT VA IN INJECTED AREAS

GENE THERAPY FOR LCA

GENE THERAPY FOR LCA

NO ADVERSE LONG TERM COMPLICATIONS

AT ONE YEAR THE VA HAD NOT CHANGED BUT ALL 3 COULD SEE VERY DIM LIGHTS AND ONE COULD READ AN ILLUMINATED CLOCK WITH ECCENTRIC FIXATION

GENE THERAPY FOR LCA

NEI SPENT $124 MILLION BETWEEN 1993 - 2007 FOR THE BASIC RESEARCH AND $3.7 MILLION ON THE CLINICAL TRIAL

ONLY TYPE 2 LCA HAS THE RPE65 GENE AND IS ONLY 6% OF CASES OF LCA

GENE THERAPY FOR LCA

LANCET 2009 MAGUIRE ET AL

12 PATIENTS GIVEN RPE65 . AGE RANGE 8 -44. 2 YEAR FOLLOW UP. STUDY LOOKED AT AGE AND DOSE.

ALL HAD IMPROVEMENT IN VF AND PUPILLARY RESPONSE

LCA

GENE THERAPY FOR LCA

GENE THERAPY FOR LCA

NEJM 5 MAY 2015 372: 1887-1897

3 YEAR RESULTS OF PHASE 1-2 TRIAL

IN HUMANS IMPROVEMENT IN RETINAL SENSITIVITY WERE MODEST AND FAILED TO PROTECT AGAINST ONGOING DEGERNERATION.

GT LEAD TO TEMPORARY,VARIABLE AND INCOMPLETE RESTORATION OF RETINAL FUNCTION.

UNMET DEMAND FOR RPE 65

GENE THERAPY FOR LCA

IN SUMMARY GENE THERAPY IS DIFFICULT BECAUSE OF THE MULTIPLE GENES INVOLVED.

NO ADVERSE EFFECTS WITH LOWER DOSES.

BEST AGE TO TREAT UNDETERMINED

CONCLUSION

IT IS MORE IMPORTANT TO KNOW THAT A PROBLEM EXISTS THAN WHAT DYSTROPY IS PRESENT

DO NOT GIVE A DIAGNOSIS.DO NOT SPECULATE BEFORE ALL TEST RESULTS ARE IN AND SECOND OPINION FROM RETINA SPECIALIST OBTAINED

CONCLUSIONS

THE 4 TESTS THAT SHOULD BE DONE ON MOST DYSTROPHIES ARE: ERG
EOG VISUAL FIELD OCT

DARK ADAPTATION WHEN POSSIBLE

CONCLUSION

FAMILY HISTORY IS VERY IMPORTANT AND PARENTS SHOULD BE ENCOURAGED TO CALL RELATIVES

RETINA SPECIALIST SHOULD GIVE DIAGNOSIS , DISCUSS STEPS IN GENE EVALUATION AND TREATMENT OPTIONS

CONCLUSION

WE ARE ABOUT TO ENTER A NEW AND EXCITING ERA IN DIAGNOSIS AND TREATMENT

EVENTUALLY MOST DISEASES AND DYSTROPHIES WILL BE DEALT WITH AT THE GENETIC OR MOLECULAR LEVEL

CASE HISTORY

A 40 YEAR OLD MOTHER HAS AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA OCCURRING WHEN SHE WAS 24 YEARS OLD. SHE HAS A KNOWN MUTATION IN HER RHODOPSIN GENE. SHE BRINGS IN HER 5 YEAR OLD AND ASKS THAT THE CHILD BE TESTED TO SEE IF HE WILL GET THE DISEASE.

# RETINAL AND CHOROIDAL DYSTROPHIES

HOWARD B. COHEN MD

# IMPACT OF CHILDHOOD BLINDNESS

- GLOBALLY THE INCIDENCE OF CHILDHOOD BLINDNESS IS 1 PER 1000
- IN 2014 THERE WERE 1.5 MILLION BLIND CHILDREN WORLDWIDE
- THIS EQUATES TO 75 MILLION PERSON YEARS OF BLINDNESS

# IMPACT OF CHILHOOD BLINDNESS

- COMBINED CATAGORIES OF LOW VISION ARE 3 - 10 TIMES MORE COMMON THEN BLINDNESS
- COST ESTIMATES 6 - 27 BILLION DOLLARS

# IMPACT OF CHILDOOD VISUAL IMPAIRMENT USA

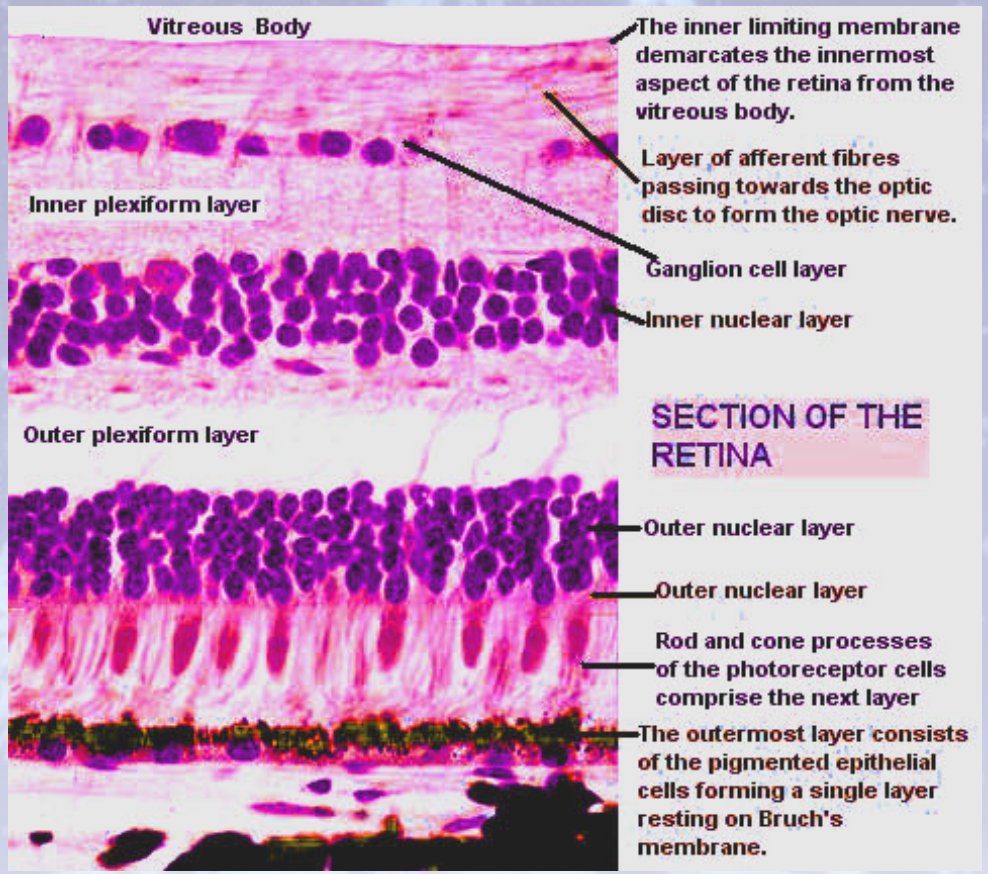
- 1% OF PERSONS UNDER 18 HAD VISUAL IMPAIRMENT NOT CORRECTED BY GLASSES
- VISUAL DISABLED AGES 4-20 = 665,200
- INFORMAL CARE PRODUCTIVITY LOSS FOR AGES 0-17 = $601,868,206

# VISUAL IMPAIRMENT

- STUDENTS WITH VISUAL IMPAIRMENT MORE LIKELY THEN OTHER STUDENTS WITH DISABLITIES TO GET A AVERAGES

- ONLY 29% OF VISUALLY IMPAIRED STUDENTS ARE EMPLOYED 3 - 5 YRS AFTER SECONDARY SCHOOL

# NORMAL RETINA



# NORMAL RETINA

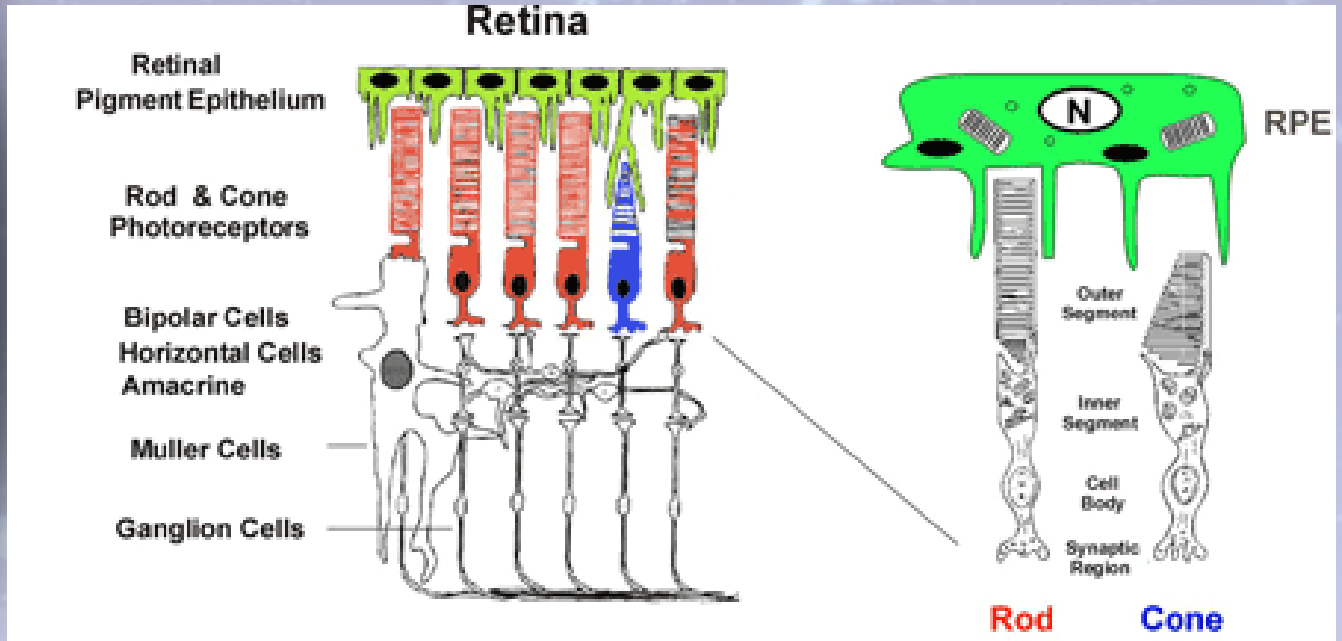
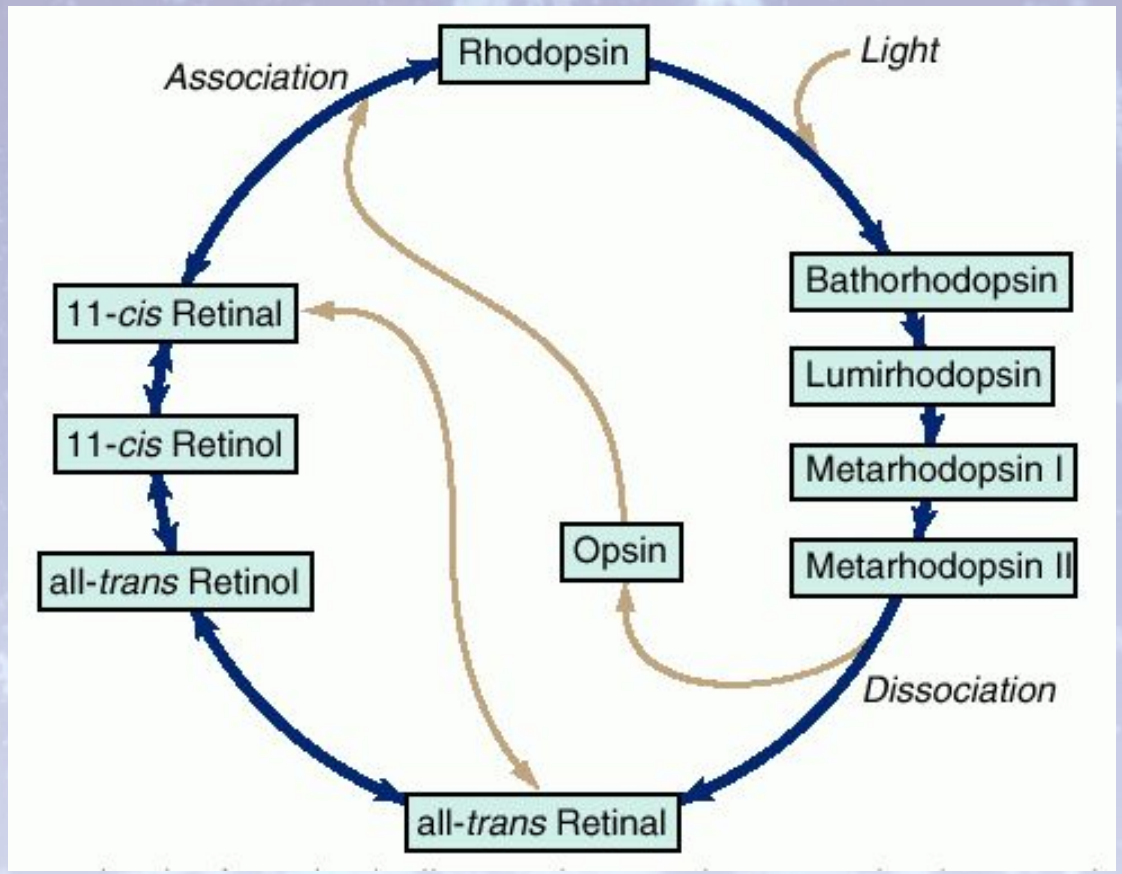
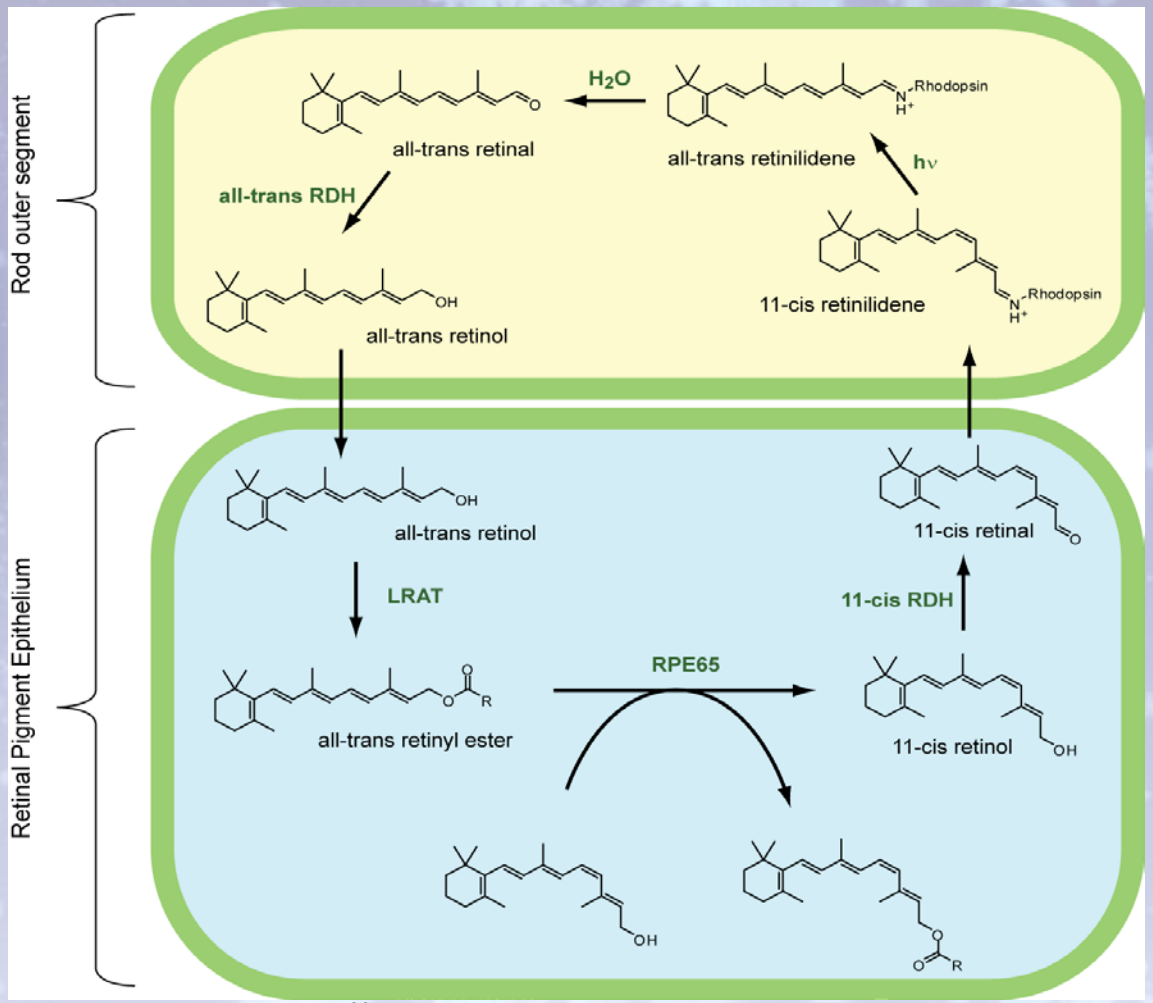



Fig 1. Diagram showing the organization of cells in the retina (left) and the rod and cone photoreceptors cells that lie against the retinal pigment epithelial cells (RPE).

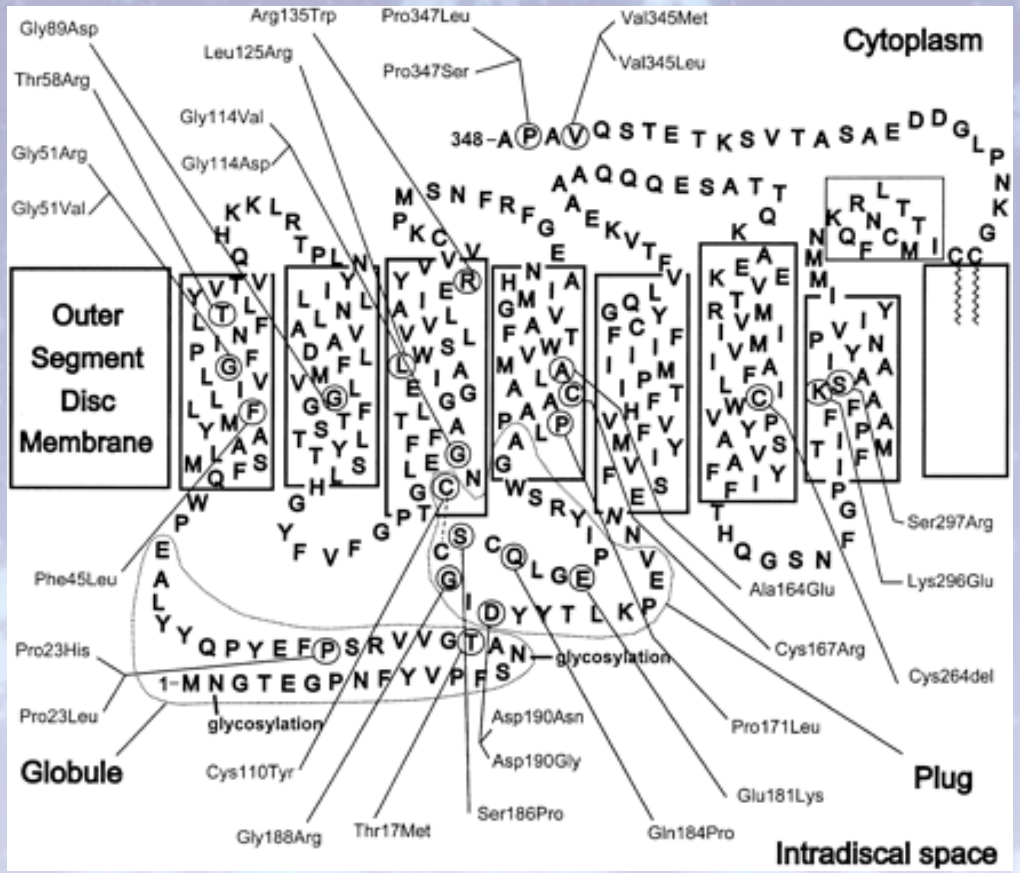
# VISUAL CYCLE



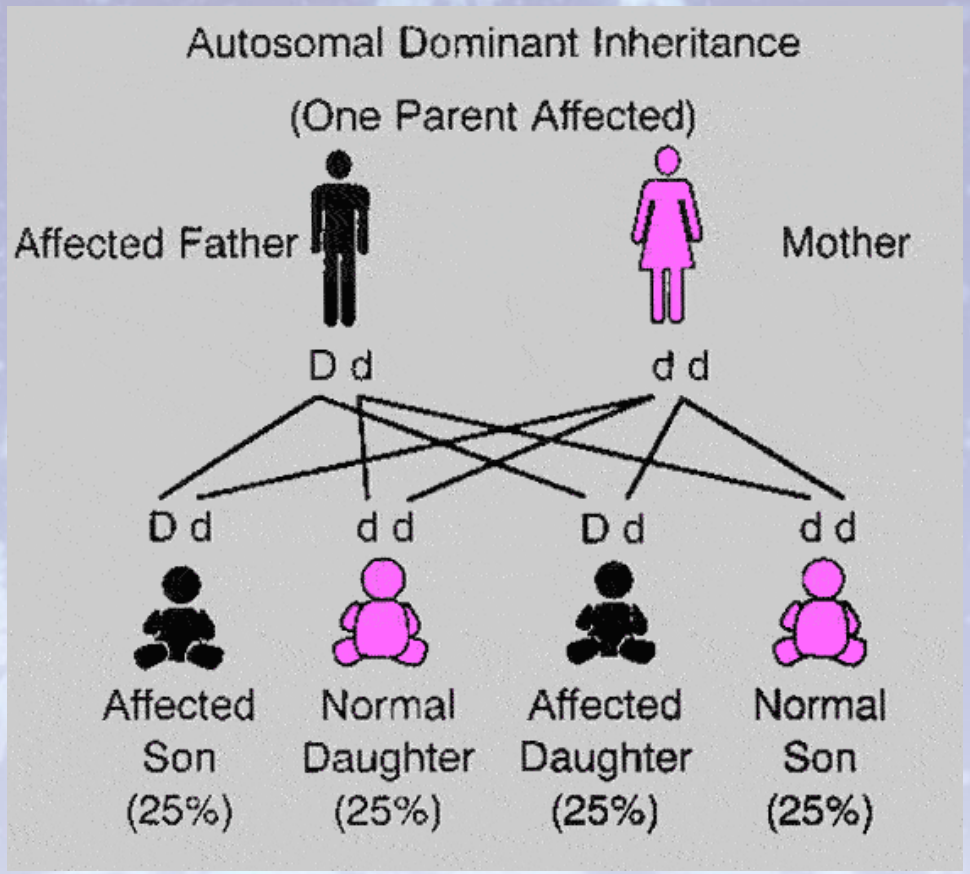
# VISUAL CYCLE



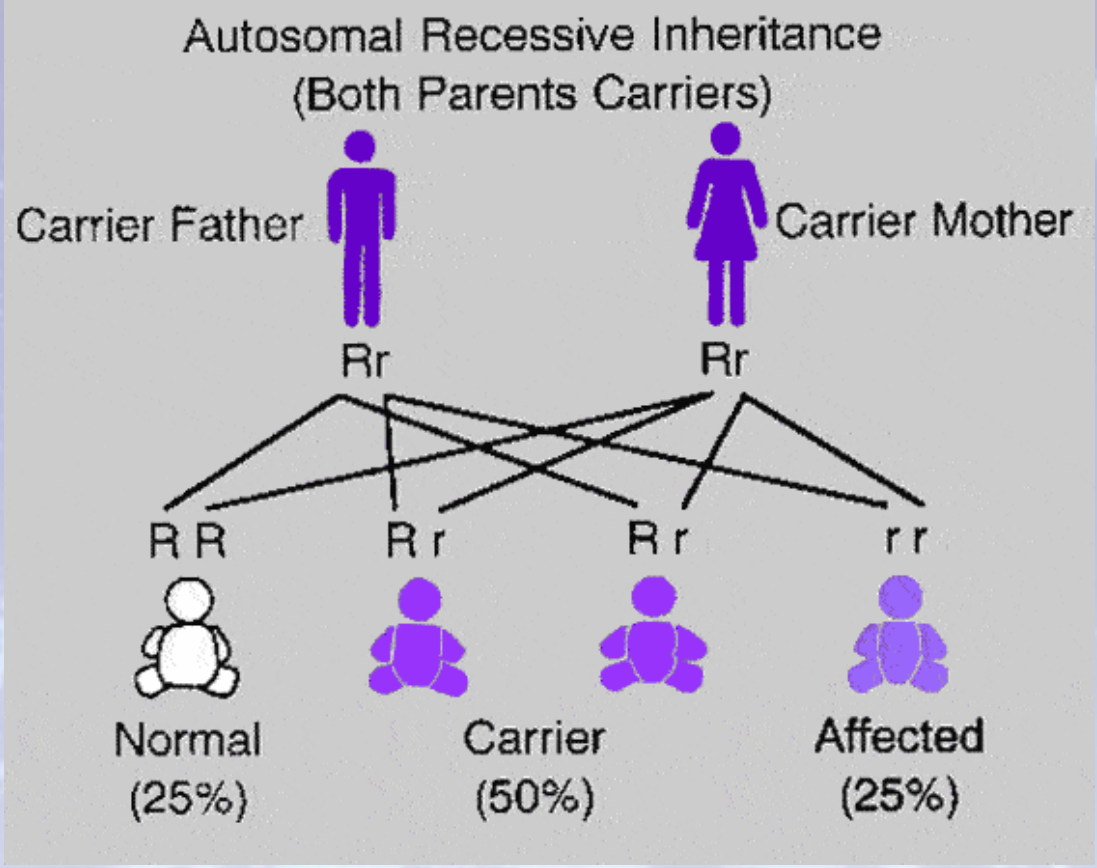
# NORMAL RETINA



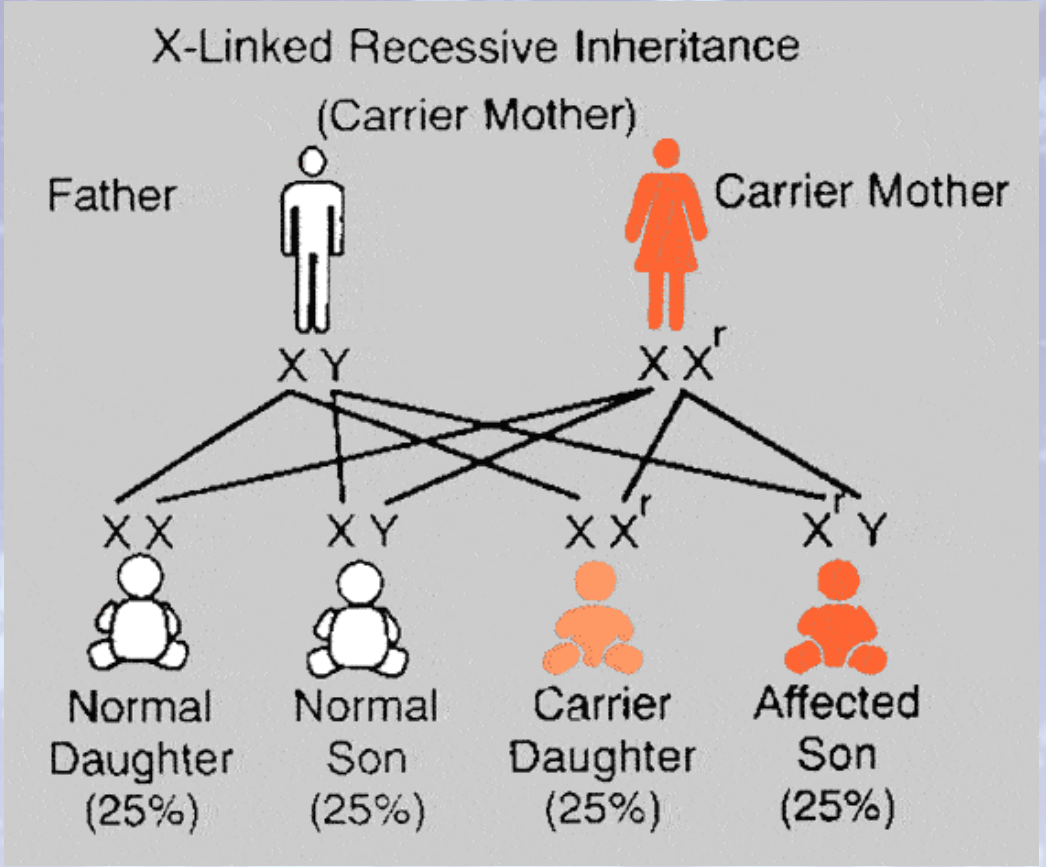
# INHERITANCE PATTERNS



# INHERITANCE PATTERNS



# INHERITANCE PATTERNS



# RETINITIS PIGMENTOSA INCIDENCE

- HIGH - 5 / 1000
- LOW - 1 / 7000
- REPRESENTS DIFFERENCES IN DISTRIBUTION AND ACCURACY OF SAMPLE
- MALES 55-60 %
- OCCURS IN ALL RACES

# HEREDITARY PATTERNS

- FREQUENCY DEPENDS ON THE METHOD USED TO COLLECT THE DATA
- ALTHOUGH SPORADIC OR ISOLATED TYPES ARE MOST COMMON MANY OF THESE ARE THOUGHT TO BE RECESSIVE

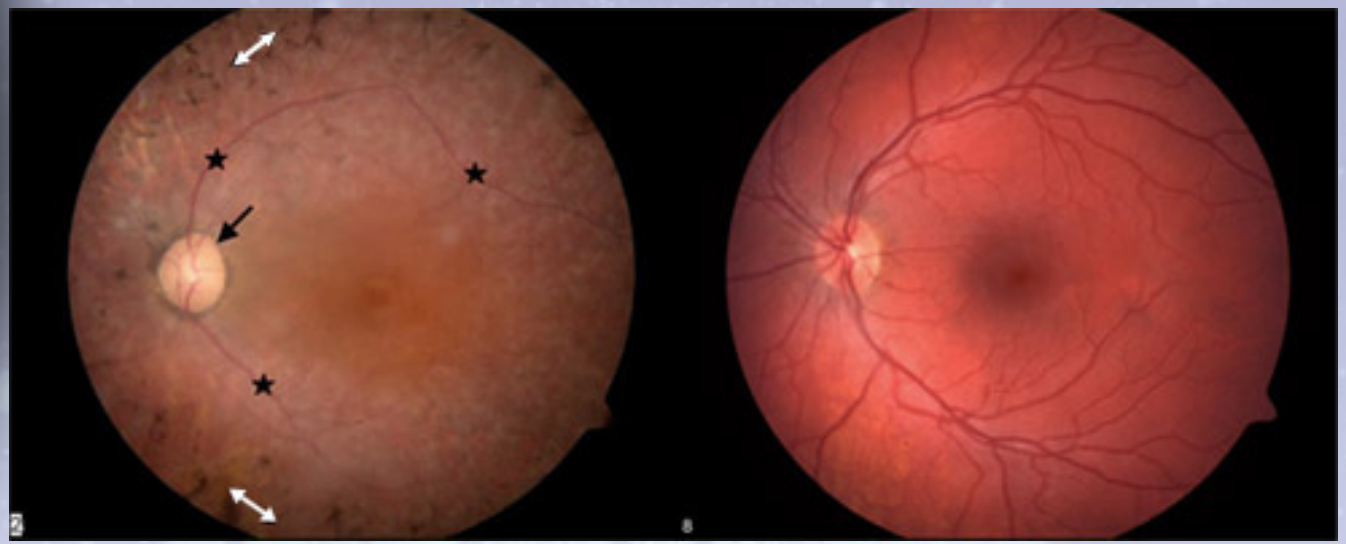
# HEREDITARY PATTERNS

- RECESSIVE IS MOST COMMON WHEN ISOLATED CASES ARE INCLUDED
- DOMINANT FOLLOWS WITH 9 TO 20%
- X - LINKED 4 - 20%

# RETINITIS PIGMENTOSA CLASSIC TRIAD

- ATTENUATION OF VESSELS
- RETINAL PIGMENTARY CHANGES
- PALLOR OF THE OPTIC NERVE

# RETINITIS PIGMENTOSA



# ATTENUATION OF VESSELS

- DEATH OF THE RODS LEADS TO LOSS OF CELL MASS IN THE NUCLEAR LAYERS AND DEGENERATION OF ASSOCIATED NEURONS

- THESE CHANGES ALLOW INCREASED OXYGEN TO REACH THE INNER RETINA

# ATTENUATION OF VESSELS

- INCREASED OXYGEN IN THE INNER RETINA LEADS TO THE ATTENUATION OF VESSELS OBSERVED IN RP

# PIGMENTARY CHANGES

- BONE SPICULES COMMON BUT NOT REQUIRED FOR THE DIAGNOSIS

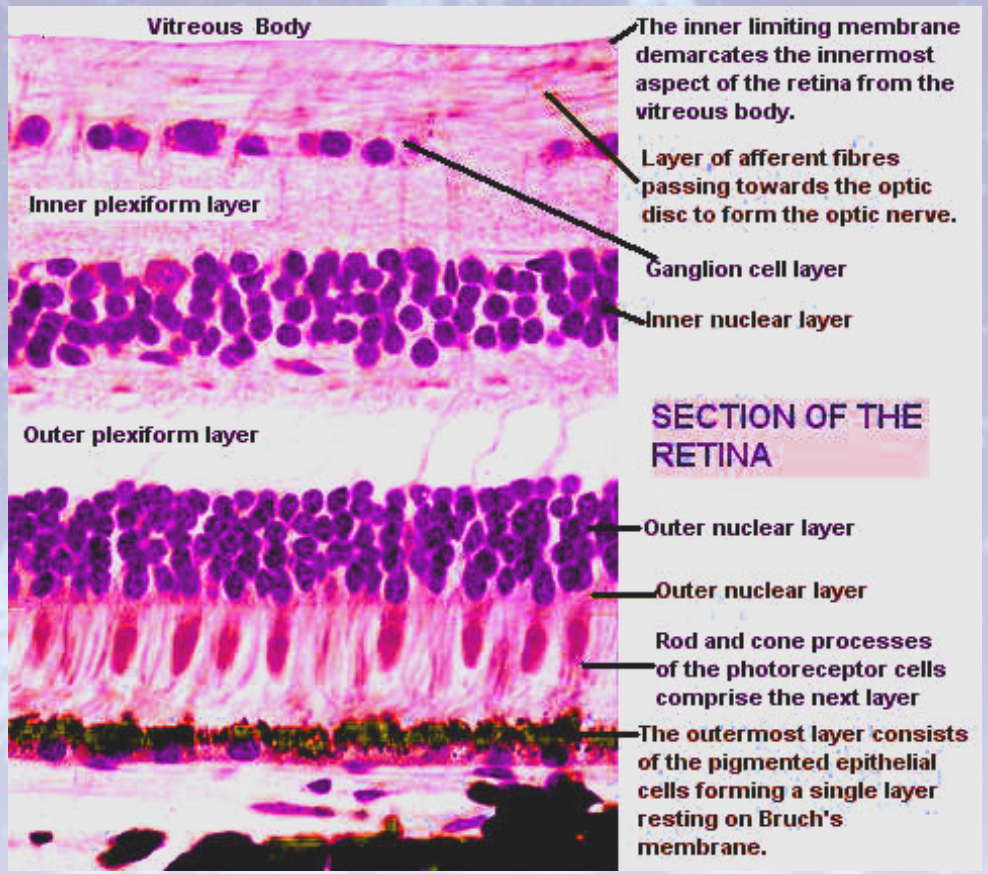
- ANIMAL STUDIES SHOW THAT BONE SPICULES DEVELOP WHEN THE RETINAL VESSELS TOUCH THE RPE

# PIGMENTARY CHANGES

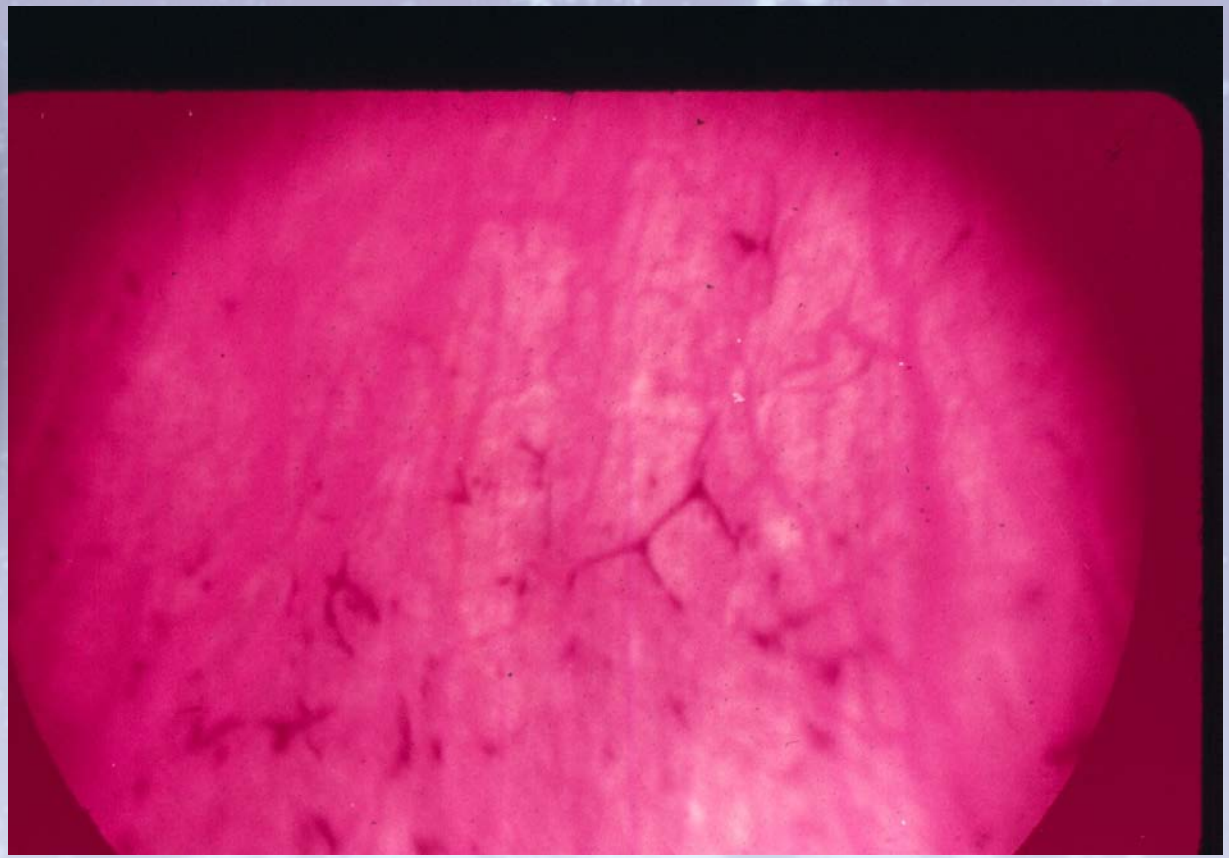
- THE AMOUNT AND SHAPE REFLECT THE RETINAL VESSELS IN THE AREA AT THE TIME.

- RPE CELL FORM AROUND THE VESSELS TO ESTABLISH AN NEW BLOOD RETINAL BARRIER

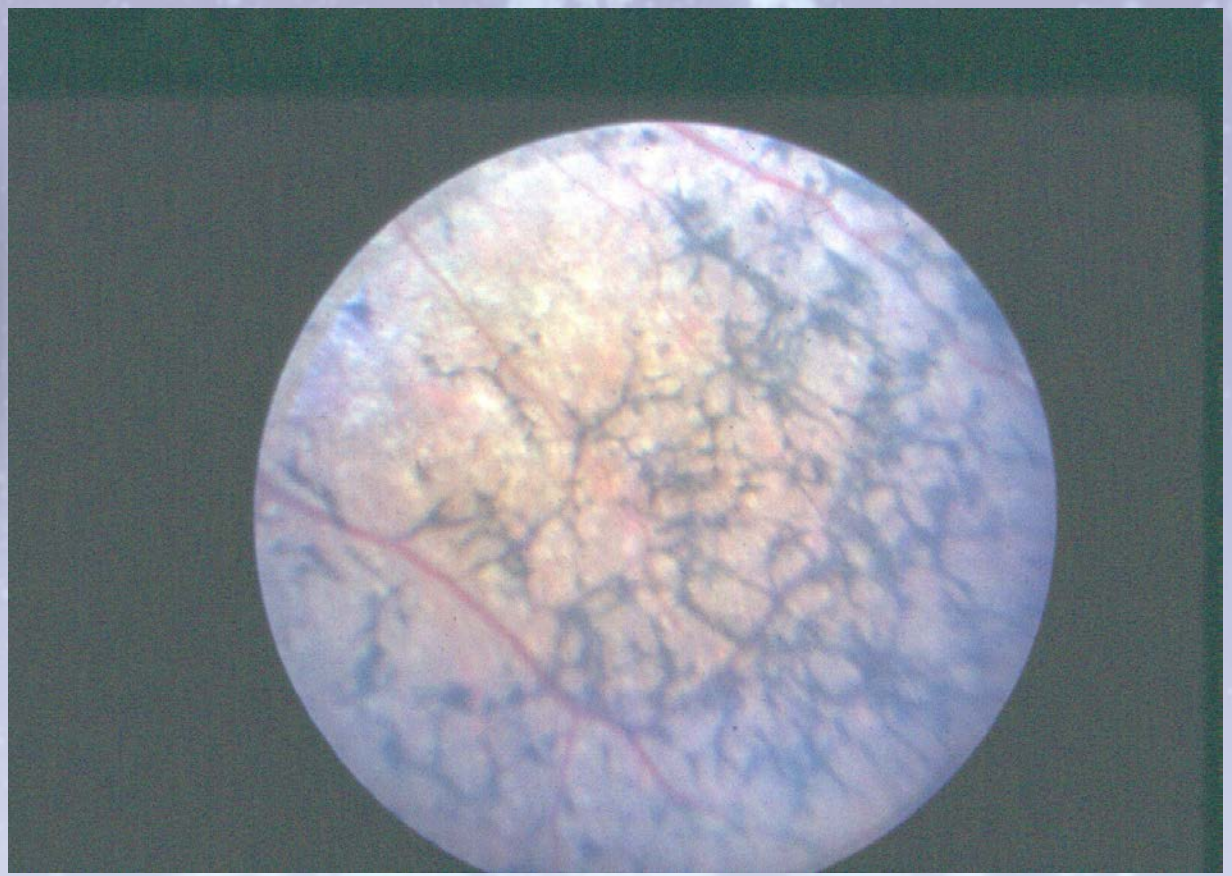
# NORMAL RETINA



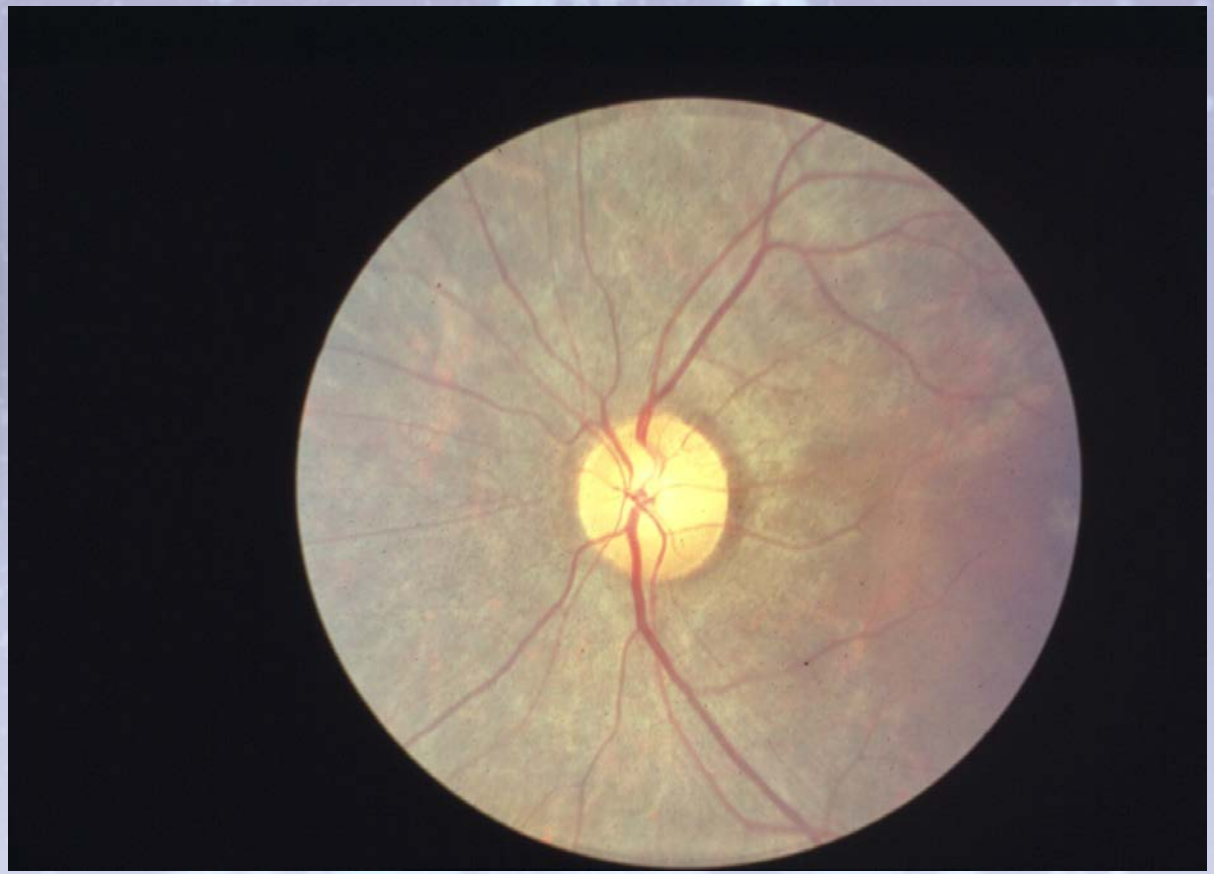
# RETINITIS PIGMENTOSA
# BONE SPICULES



# RETINITIS PIGMENTOSA
# BONE SPICULES

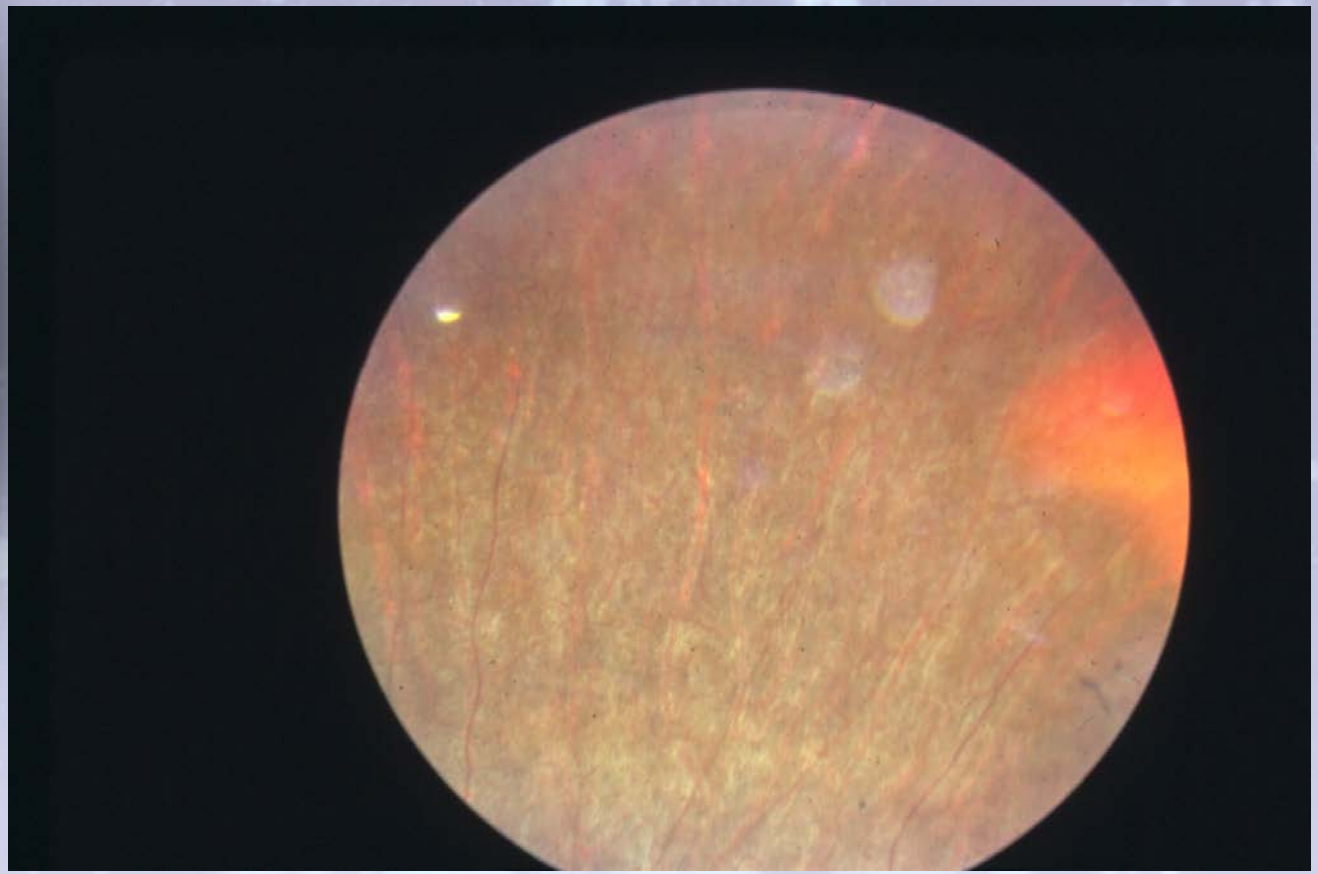


# RETINITIS PIGMENTOSA



SINE BONE SPICULES

# RETINITIS PIGMENTOSA



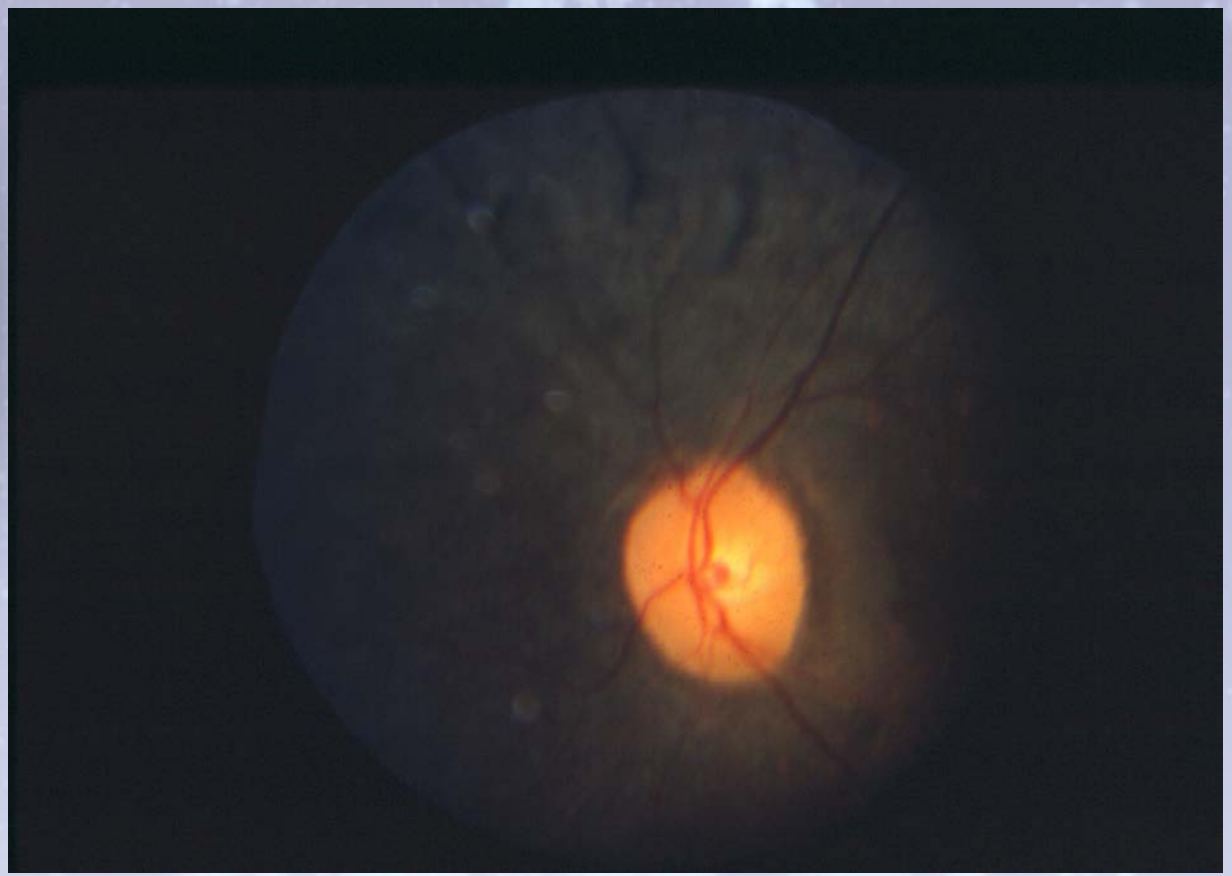
SINE BONE SPICULES

# OPTIC NERVE CHANGES

- CHANGES PARALLEL THE DEGREE OF LOSS OF PHOTORECEPTORS

- LATE THE DISC WILL HAVE A HARD , YELLOW , WAXY APPEARANCE DENOTING SECONDARY OPTIC ATROPHY

# RETINITIS PIGMENTOSA



OPTIC PALLOR

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

- ATROPHIC MOST COMMON IN PATIENTS WITH LESS THEN 20 / 200

- ATROPHY RESULTS FROM RPE DEGENERATION RESULTING FROM CME OR CONE LOSS

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

- ROD DEGENERATON LEADS TO NUTRITIONAL DEFICIENCES AND CONE DEATH DRIVEN BY THE INSULIN/MTOR PATHWAY

- MAMMALIAN TARGET OF RAPAMYCIN PATHWAY

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

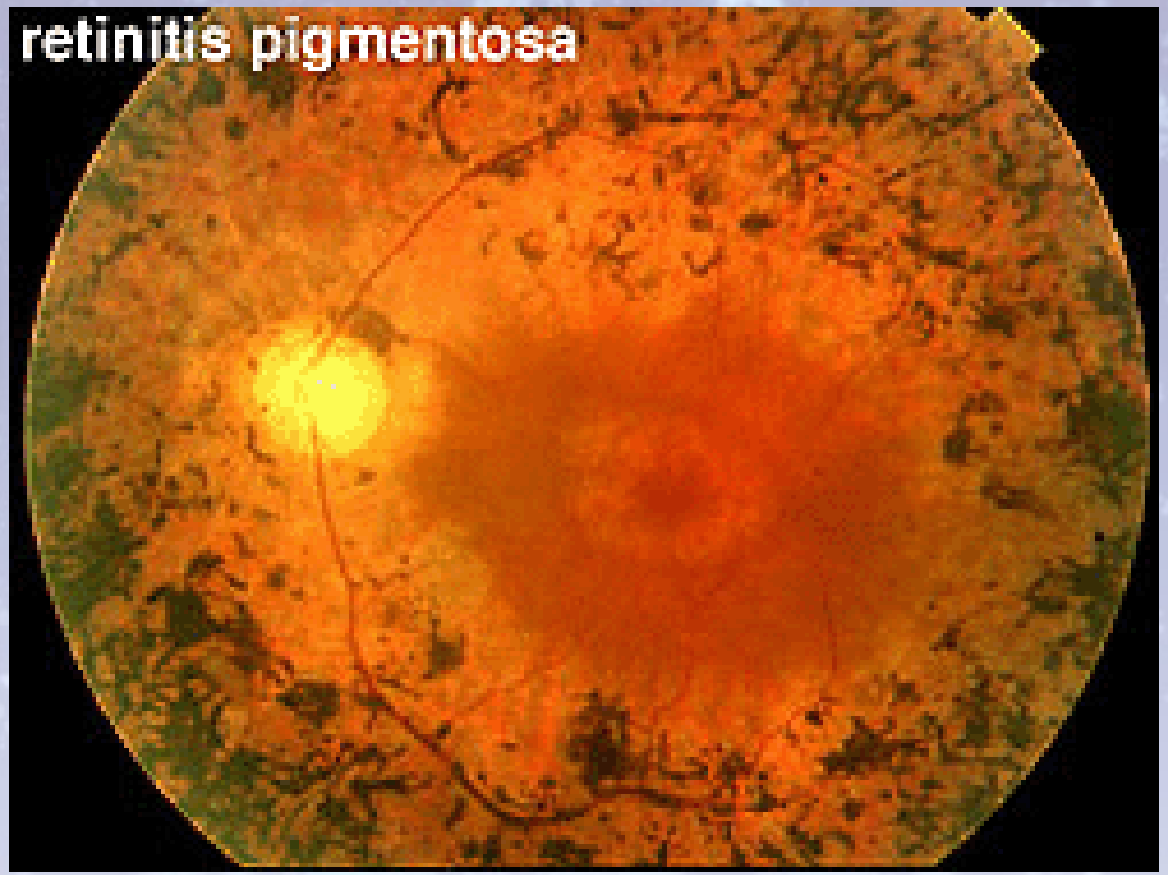
- SOME INVESTIGATORS BELIEVE THAT RODS PRODUCE A CONE PROTECTIVE FACTOR AND LOSS OF RODS AND THIS FACTOR RESULTS IN LOSS OF CONES

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

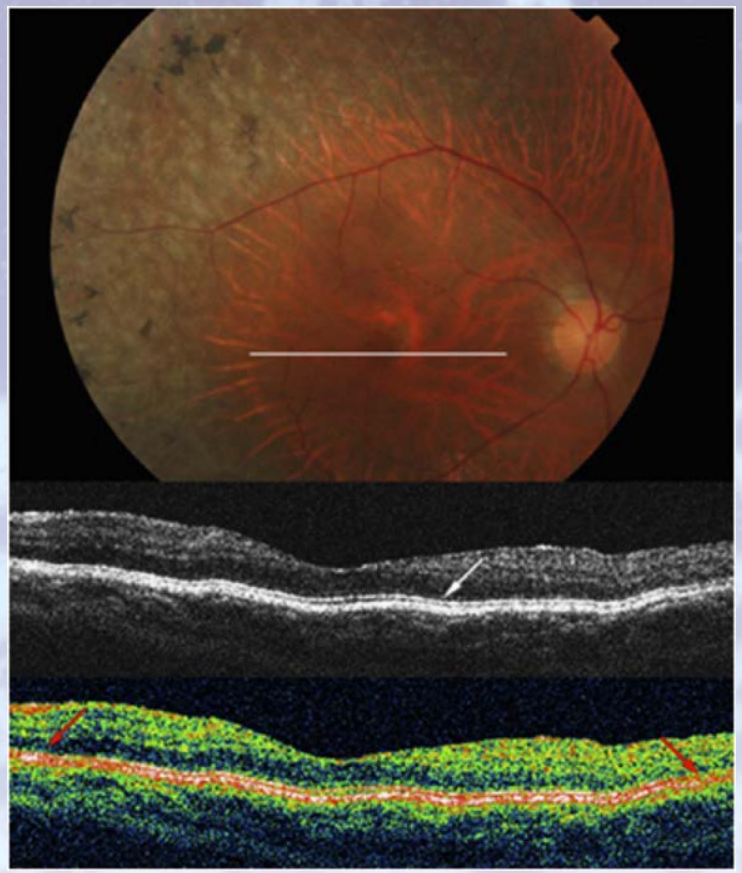
- INVESTIGATORS FROM JOHNS HOPKINS FOUND THAT CONES DIE FROM OXIDATIVE DAMAGE.

- ANTIOXIDANTS IMPROVED CONE FUNCTION AND DENSITY

# RETINITIS PIGMENTOSA



# MACULAR CHANGES IN RETINITIS PIGMENTOSA



# CME IN RP

- CME PRESENT IN 13 - 70%
- 25% HAVE 20/25 OR BETTER VA
- WIDTH OF TOTAL AREA OF CYSTOID CHANGES IS SIGNIFICANTLY CORRELATED WITH VISION

# CME IN RP

- BREAKDOWN OF BRB
- FAILURE OF PUMPING OF RPE CELLS
- MULLER CELL DYSFUNCTION
- ANTI RETINAL ANTIBODIES
- VITREOUS TRACTION
- MISC

# CME IN RP

- OCT IS DIAGNOSTIC MODALITY OF CHOICE
- CME MAY RESULT FROM LEAKAGE FROM PERIFOVEAL CAPILLARIES OR FROM MORE PERMEABLE RPE

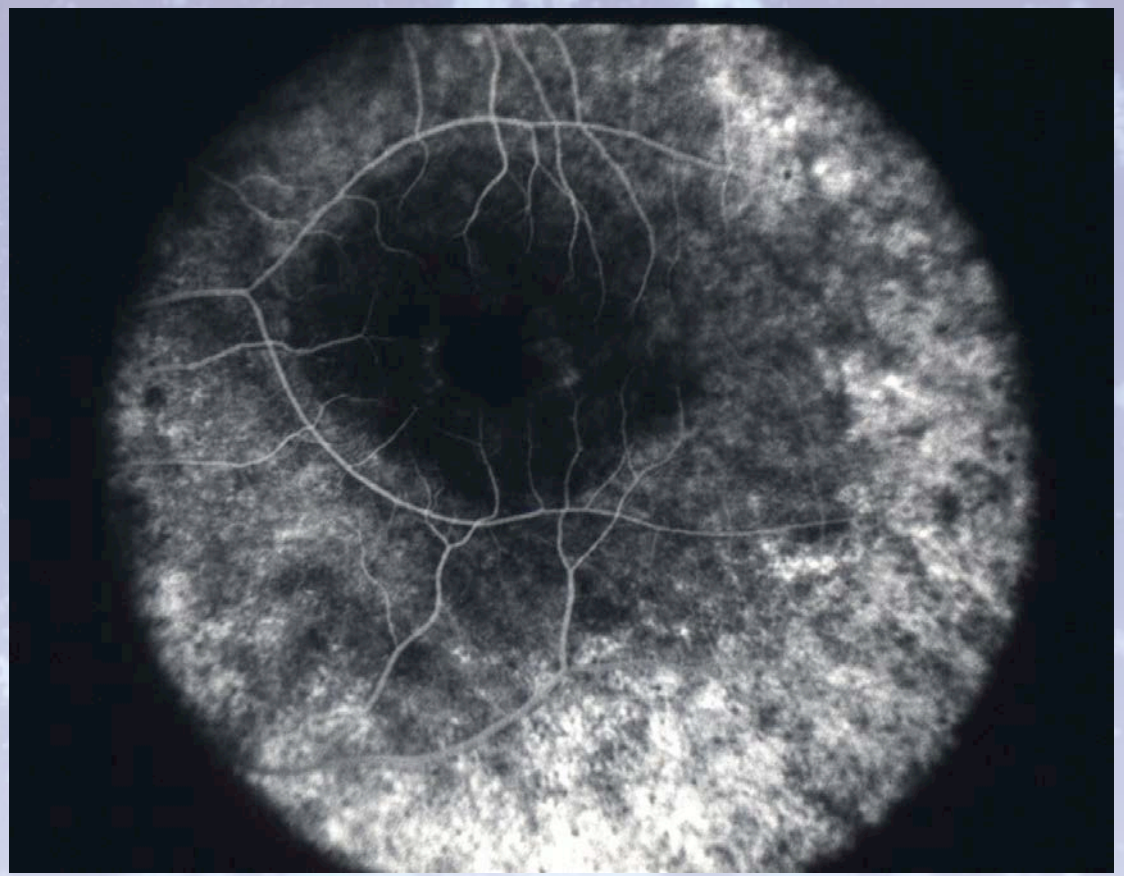
# CME IN RP

- HAJANI BJO 2008 STUDIED PREVALENCE OF CME IN RP
- 124 PATIENTS WITH RP. 38% UNILATERAL AND 27% OU WITH CME
- AD - 52%, AR 39%,ISOLATED 39%, USHER'S 35%,XLINKED 0

# CME IN RP

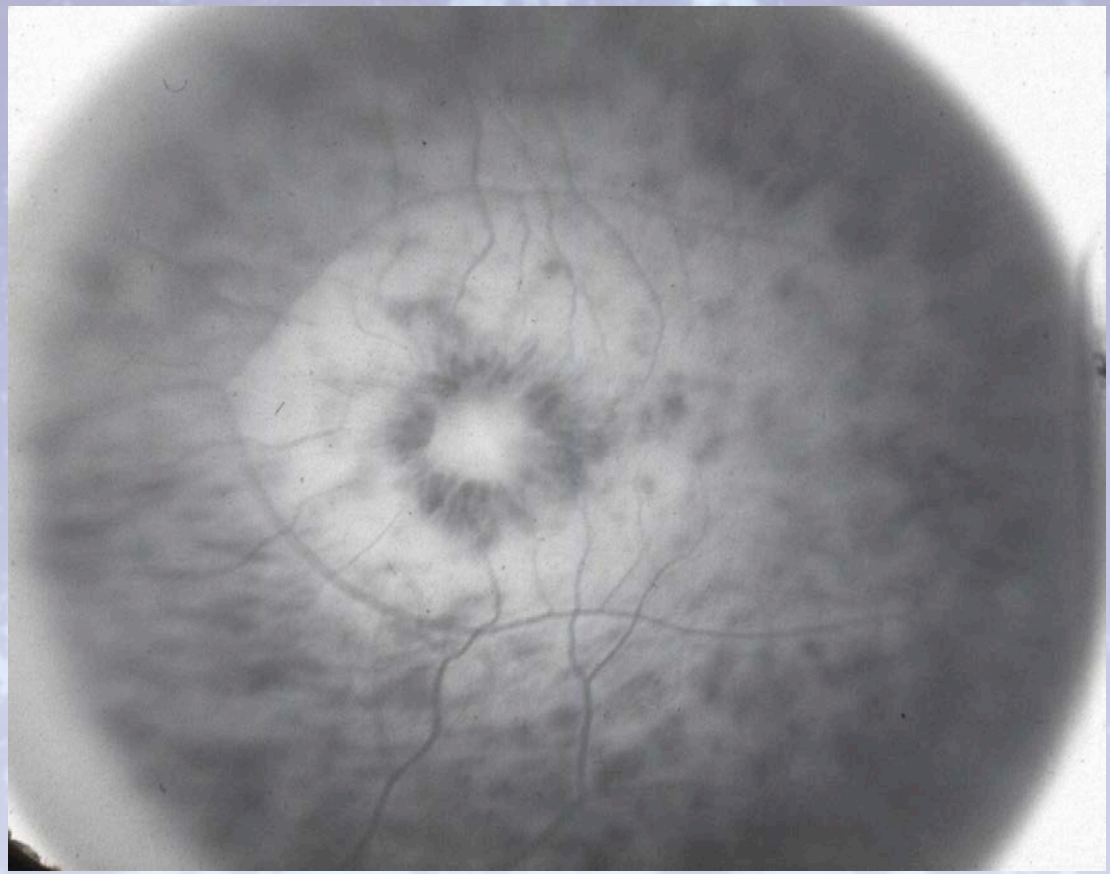
- HAJANI, EYE 2009 FOUND THAT OCT CAN REVEAL CME WHEN OPHTHALMOSCOPY OR CTL DID NOT.
- 50 PATIENTS . 20(32%)UNILATERAL AND 11 (18%) OU HAD CME ON OCT

# RETINITIS PIGMENTOSA



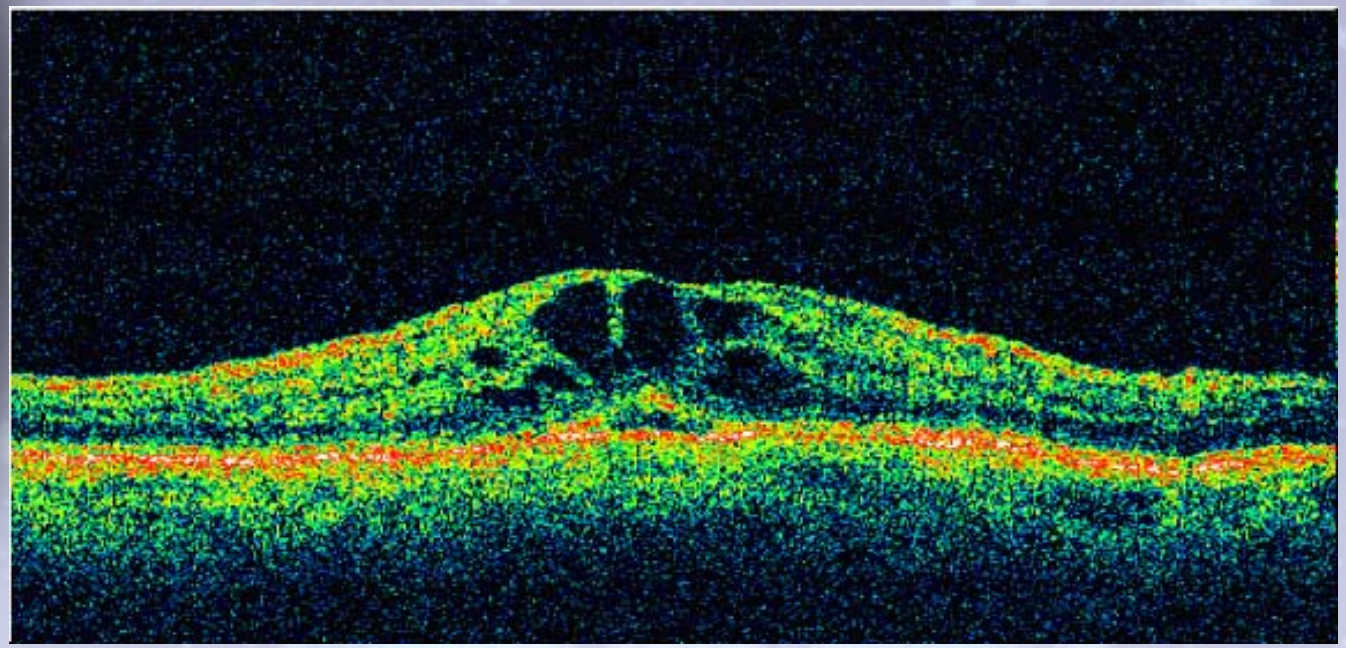
CME EARLY PHASE FA

# RETINITIS PIGMENTOSA



CME LATE PHASE FA

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

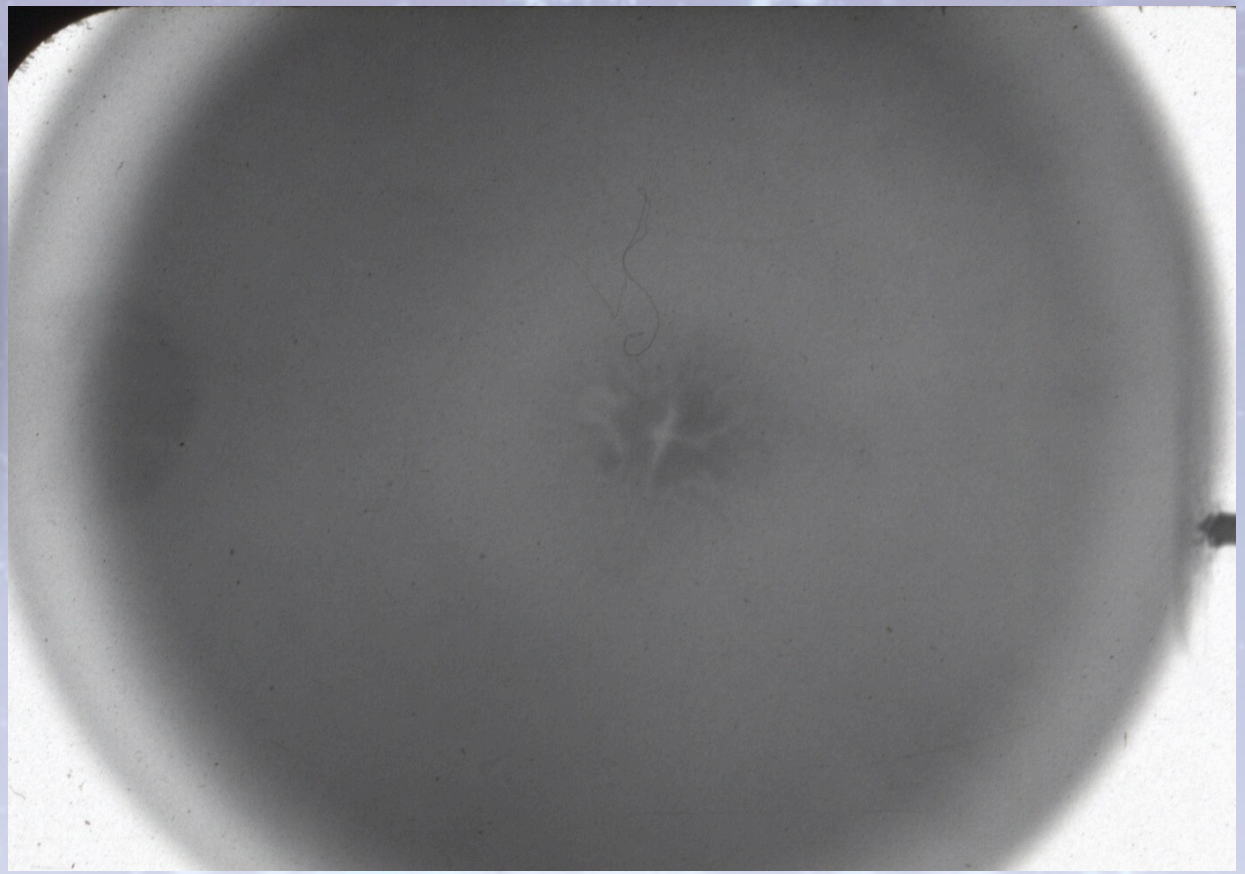


# MACULAR CHANGES IN RETINITIS PIGMENTOSA

- MANY CASES OF ATROPHIC MACULAR ARE RESULT OF LONG STANDING CME

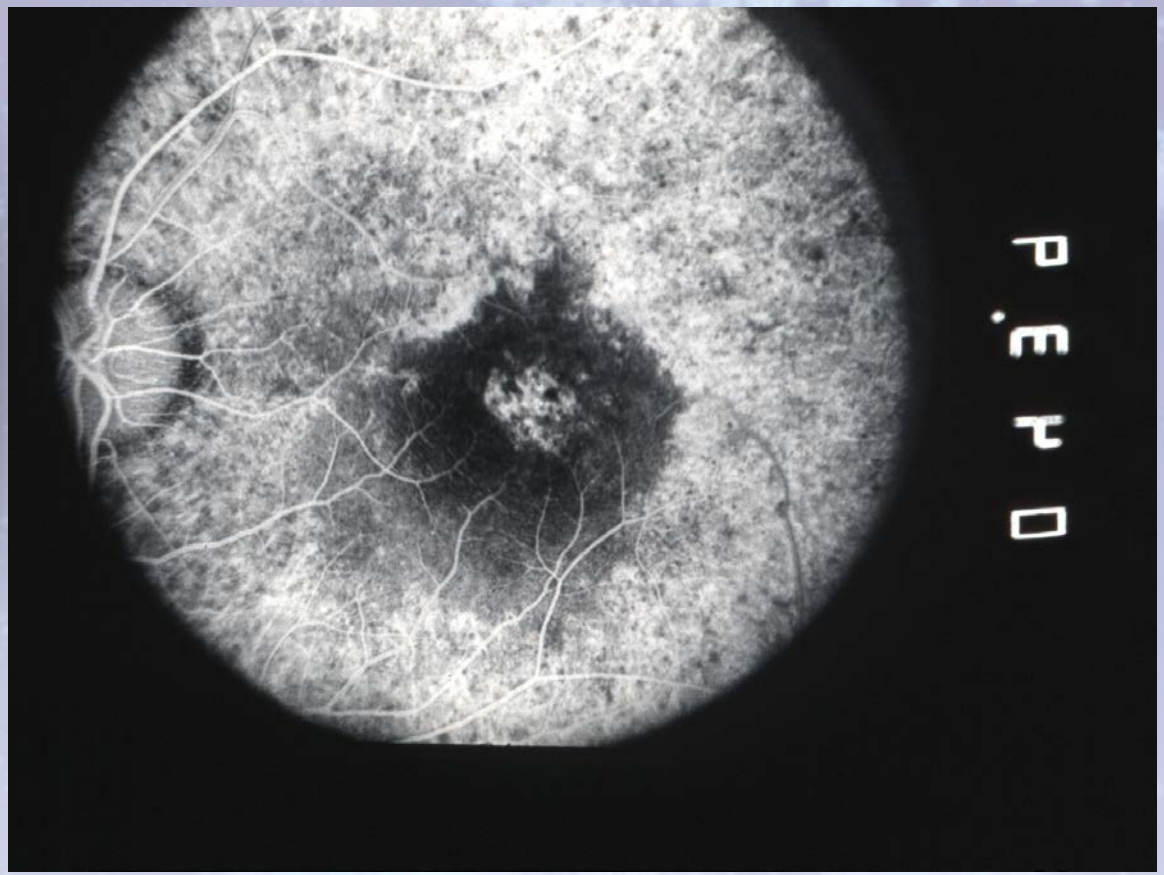
- OPHTHALMIC SURGERY 2010. PATIENTS WITH 20/200 OR WORSE .19% CME , 81% ATROPHIC

# RETINITIS PIGMENTOSA



CME

# RETINITIS PIGMENTOSA

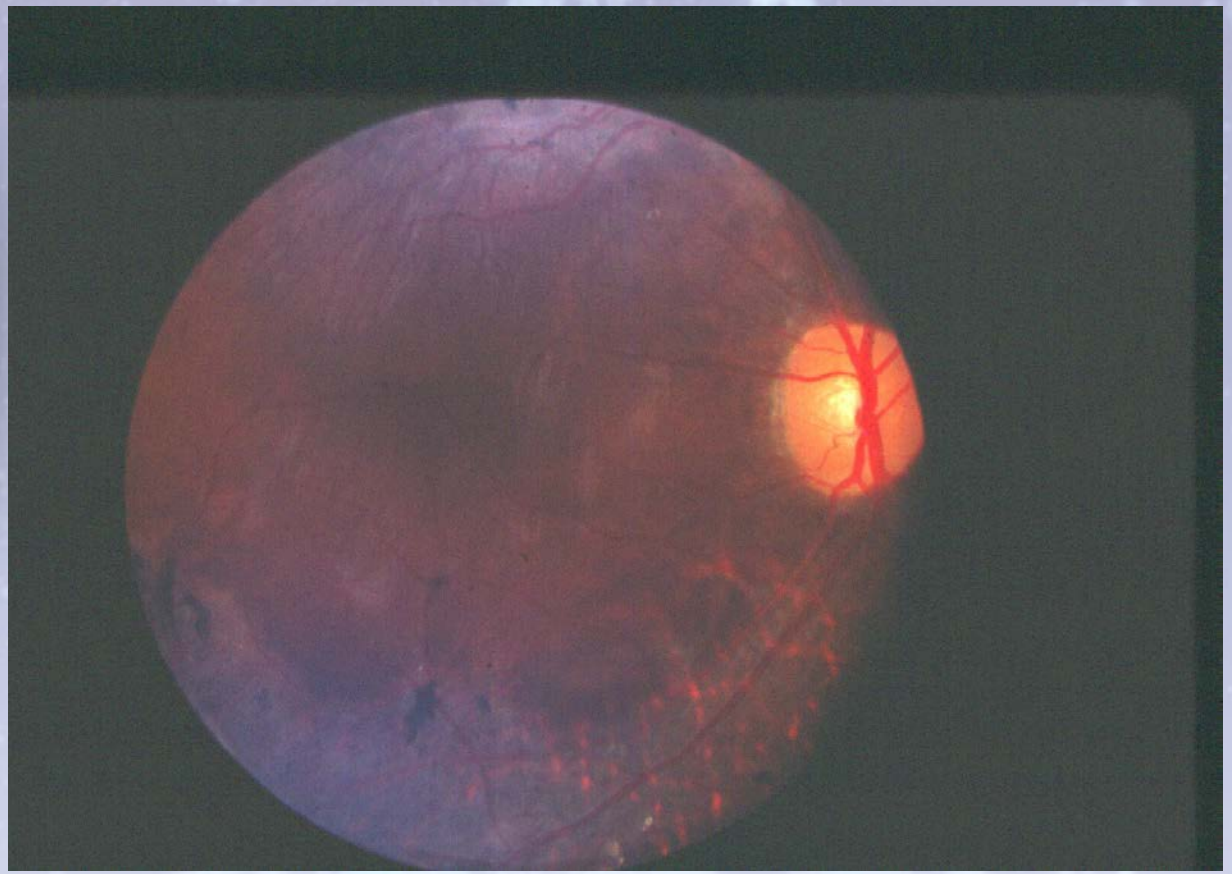


ATROPHY IN CENTRAL MACULAR AFTER RESOLUTION OF CME

# MACULAR CHANGES IN RETINITIS PIGMENTOSA

- EPIRETINAL MEMBRANE NOT UNCOMMON
- SRNV

# RETINITIS PIGMENTOSA

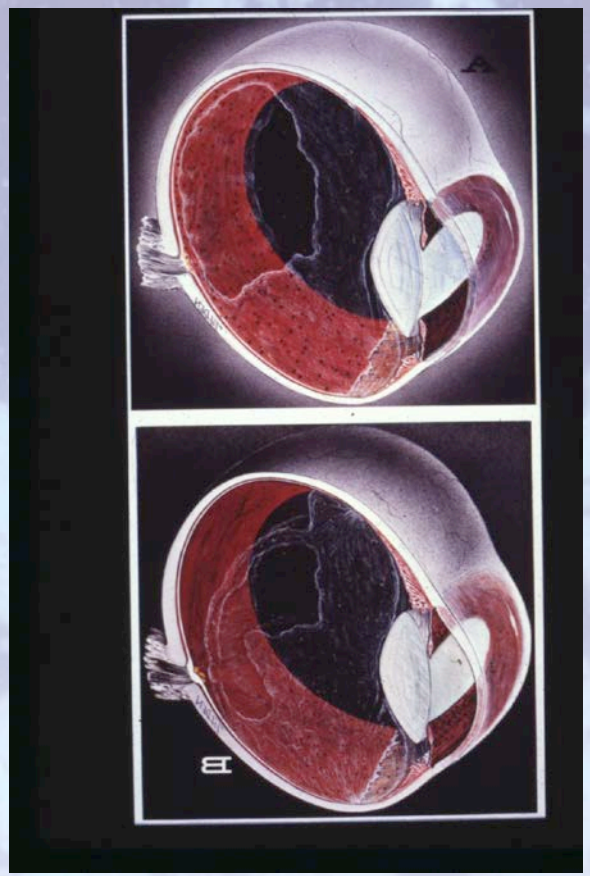


EPI RETINAL MEMBRANE

# ASSOCIATED FINDINGS

- VITREOUS OPACITIES - PRUETT EXAMINED 116 PATIENTS WITH RP AND ALL HAD OPACITIES.
- OPACITIES INCREASE WITH AGE AND HAVE NO AFFECT ON VISION

# RETINITIS PIGMENTOSA



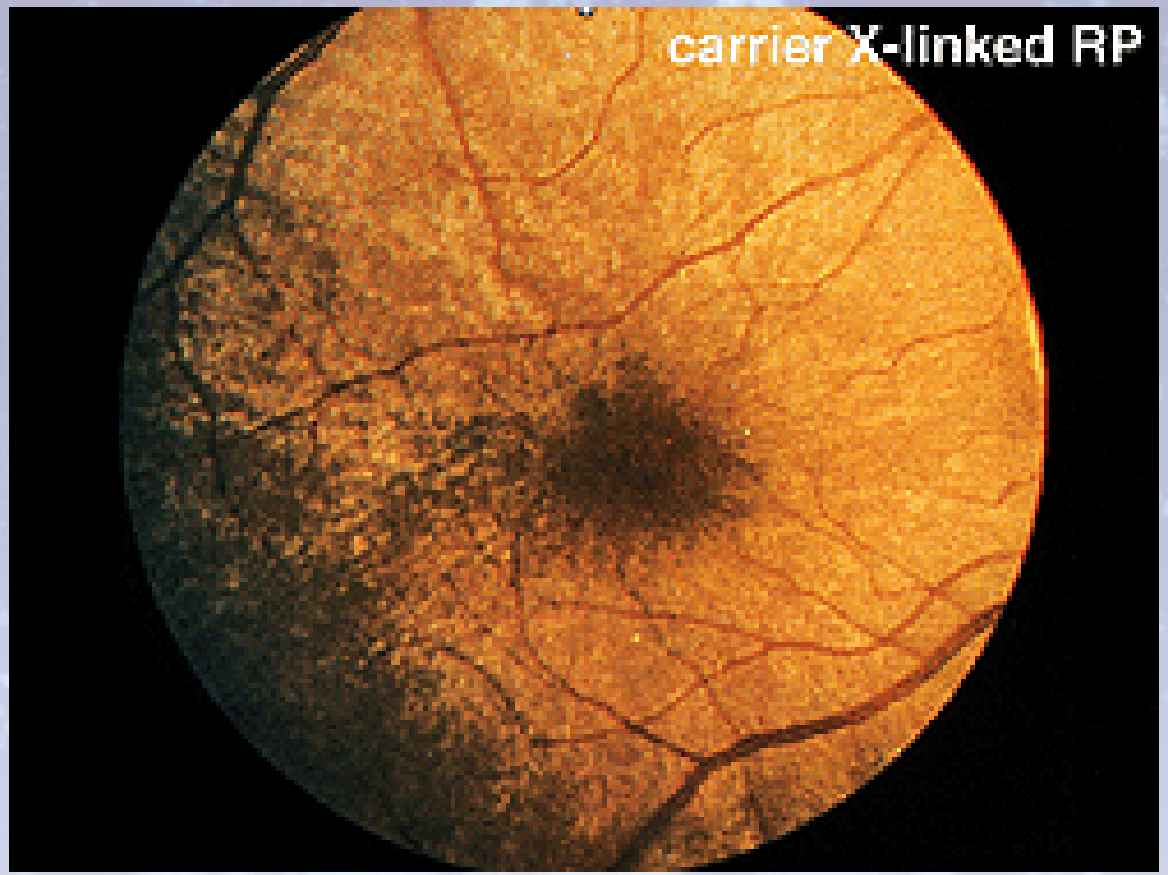
# ASSOCIATED FINDINGS

- PSC FOUND IN 11 - 20%
- PRESENT IN 60% OF RP PATIENTS OVER 40
- INCREASED INCIDENCE OF MYOPIA

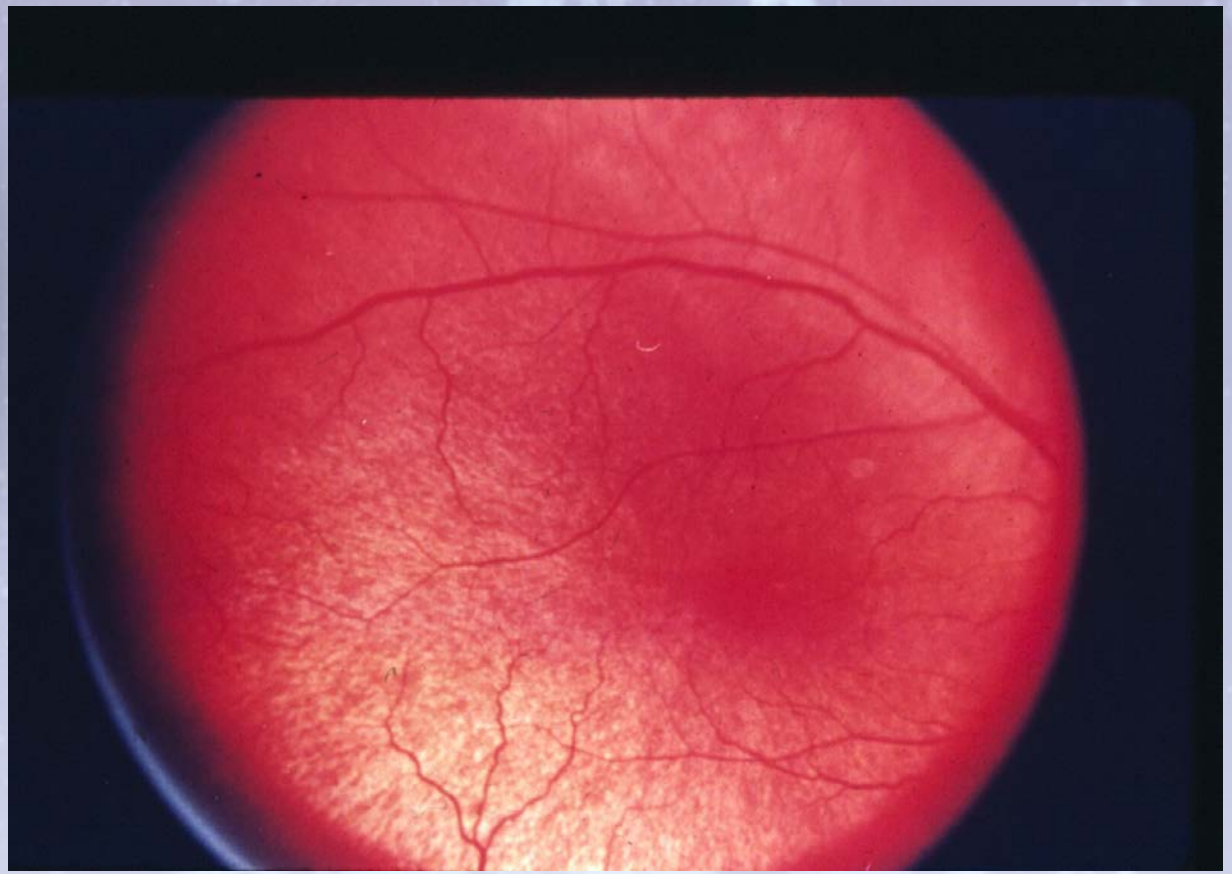
# X LINKED CARRIERS

♏X - LINKED CARRIER (FEMALES) MAY HAVE VARIABLE CHANGES IN THE RPE. ALL FEMALES IN AN RP FAMILY SHOULD HAVE A DILATED , CAREFUL FUNDUS EXAM.

# X LINKED CARRIER



# X LINKED CARRIER



X LINKED CARRIER

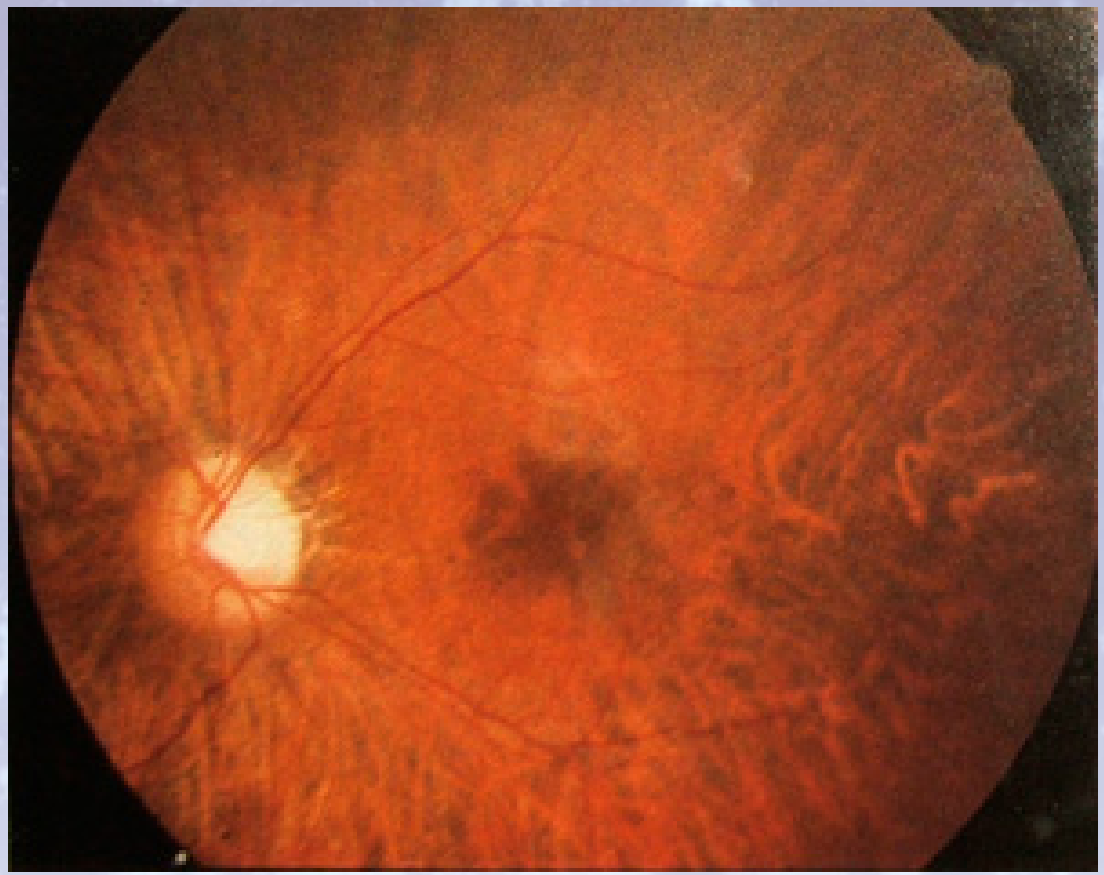
# X LINKED CARRIERS

- ERG ABNORMAL IN 54 - 96%
- EOG ABNORMALITY ALONE IN 6.5%
- OCT SHOWS INCREASED REFLECTIVITY FROM RPE

# SINE PIGMENTO

- PIGMENT CHANGES ARE OFTEN VERY SUBTLE.
- FA WILL OFTEN REVEAL SOME PIGMENT CHANGES
- MAY BE EARLY FORM OF DISEASE AS INCIDENCE IS HIGHER WITHIN FIRST 3YRS OF DIAGNOSIS

# SINE PIGMENTO



SINE PIGMENTO

# UNILATERAL

- MUST HAVE EXTINGQUISHED ERG IN AFFECTED EYE AND NORMAL IN OTHER EYE
- MOST ARE ISOLATED CASES
- OFTEN PROGRESSES TO BILATERAL

# UNILATERAL

- MUST BE FOLLOWED FOR 5 YEARS BEFORE MAKING THE DIAGNOSIS

- 100 VALID CASES REPORTED

# INVERSE

- VERY UNCOMMON AND MAY BE MISDIAGNOSED CONE DYSTROPHY

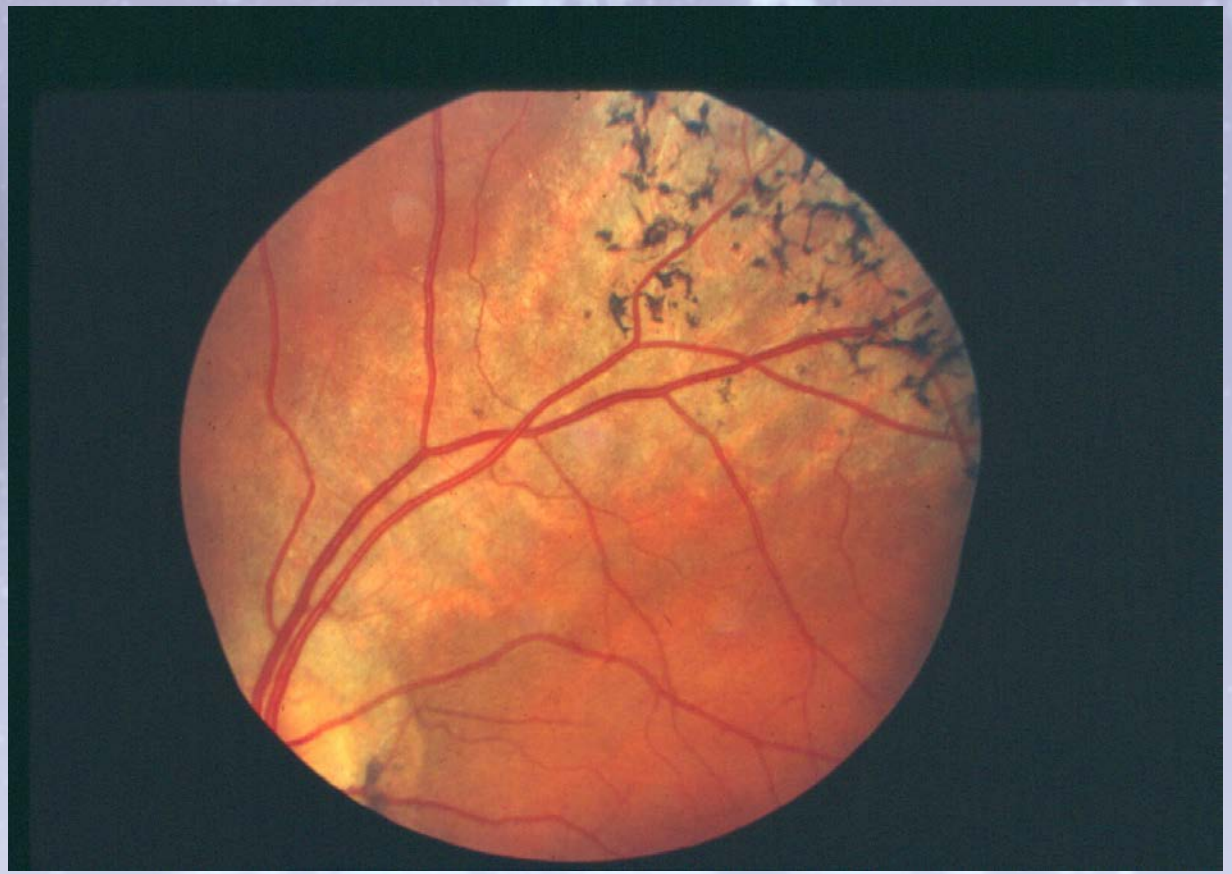
# SECTOR

- DOMINANT OR RECESSIVE
- INFERIOR QUADRANTS IN 50%
- INFERIOR NASAL NEXT MOST COMMON
- USUALLY SYMMETRICAL
- DARK ADAPTATION MAY BE NORMAL

# SECTOR

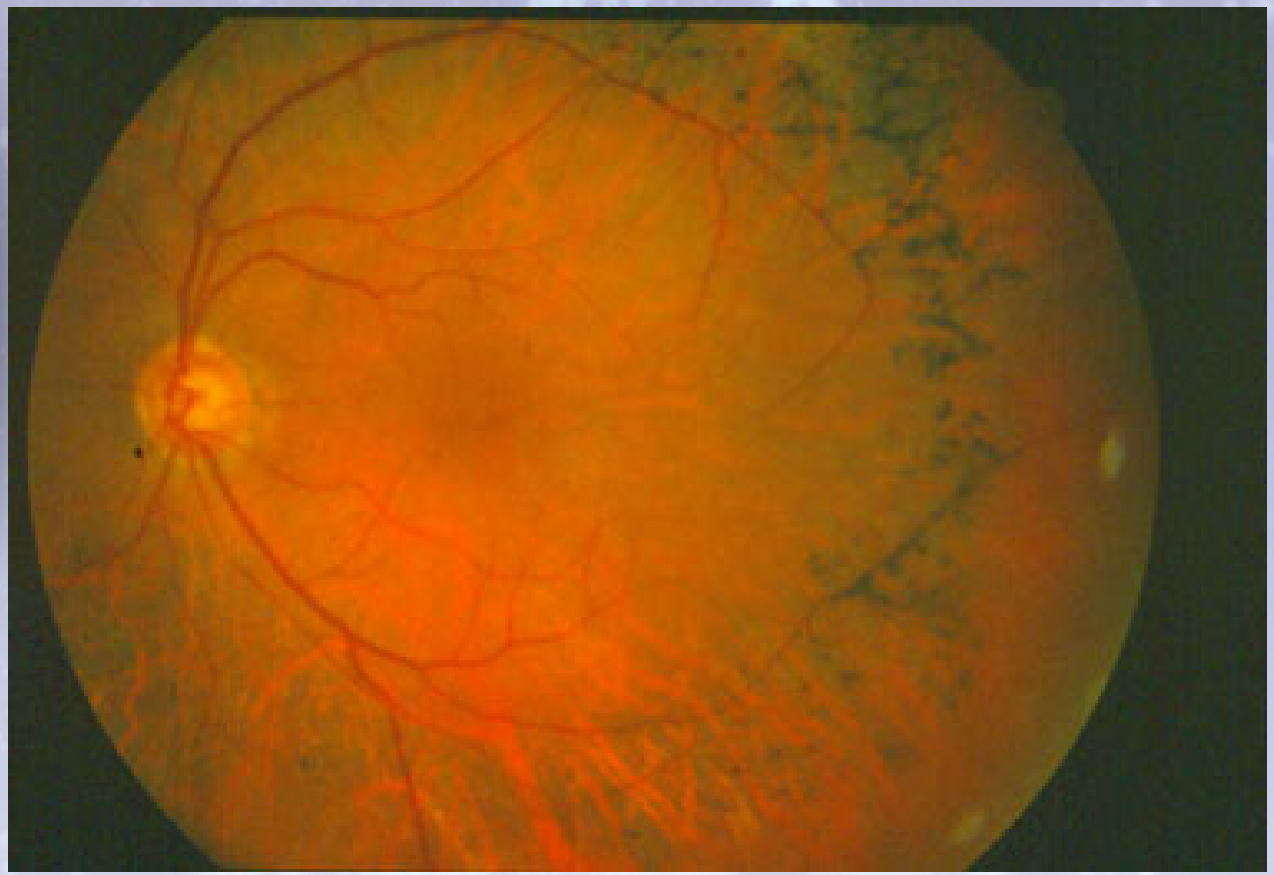
- IF BOTH NASAL QUADRANTS ARE INVOLVED A BITEMORAL FIELD DEFECT IS PRESENT
- ERG SUBNORMAL
- CAN BE ASYMPTOMATIC UNTIL 5 - 6TH DECADE
- DEAFNESS IN MANY CASES

# RETINITIS PIGMENTOSA



SECTOR

# RETINITIS PIGMENTOSA

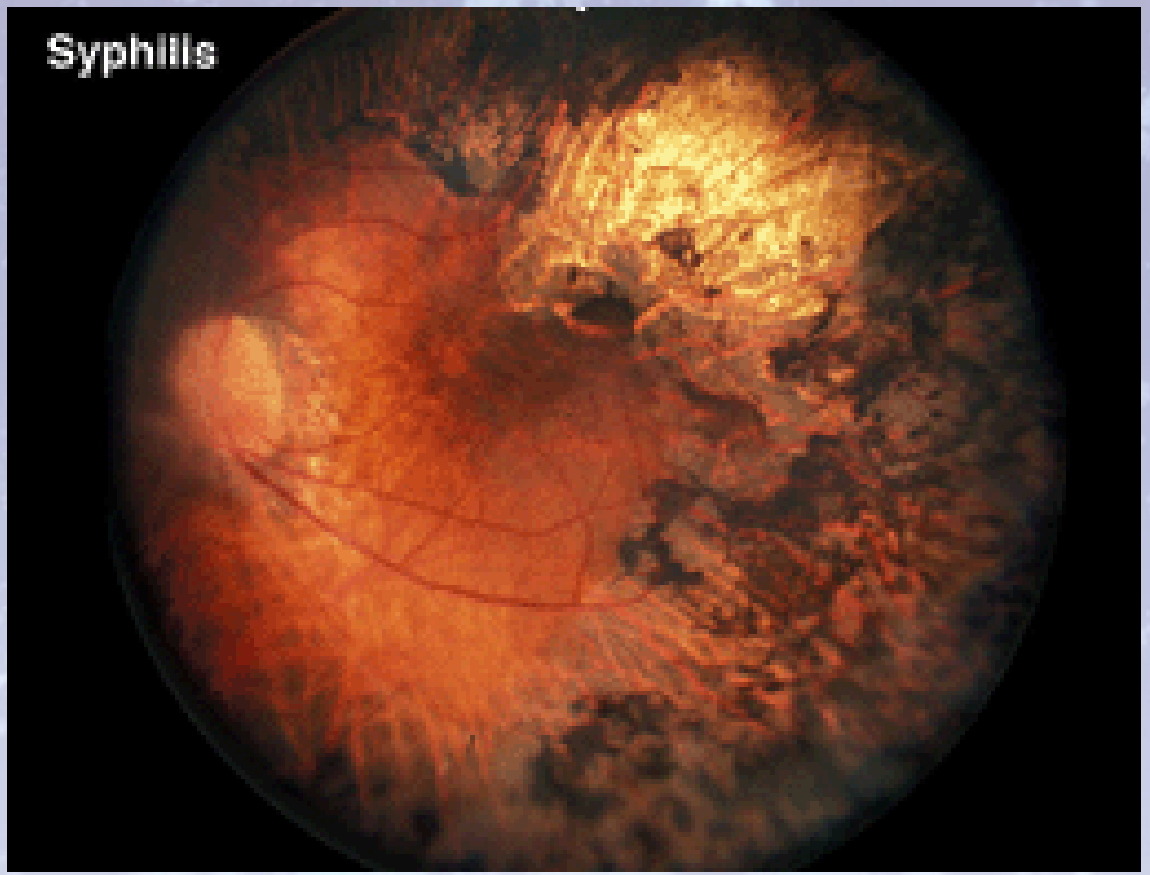


SECTOR

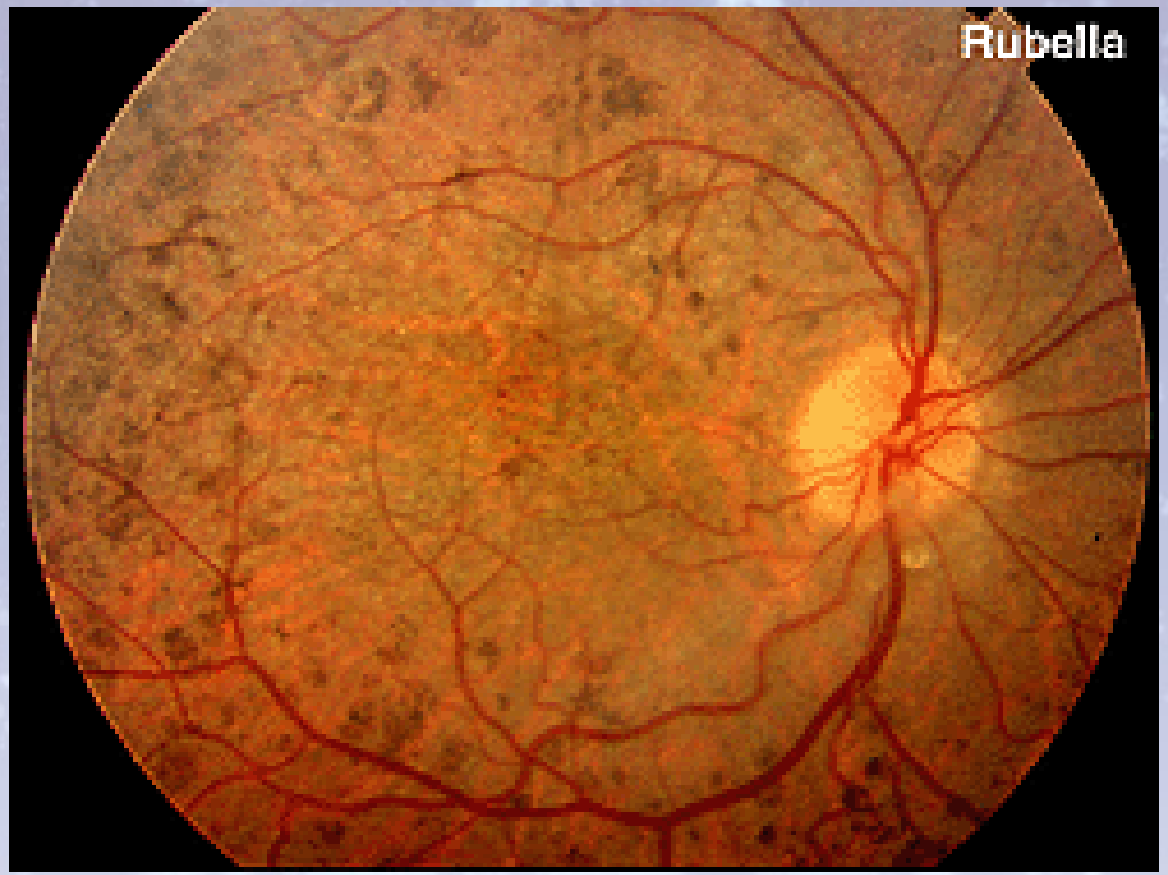
# DIFFERENTIAL

- CONGENITAL AND ACQUIRED SYPHILIS
- RUBELLA
- OTHER VIRAL
- TRAUMA
- DRUGS

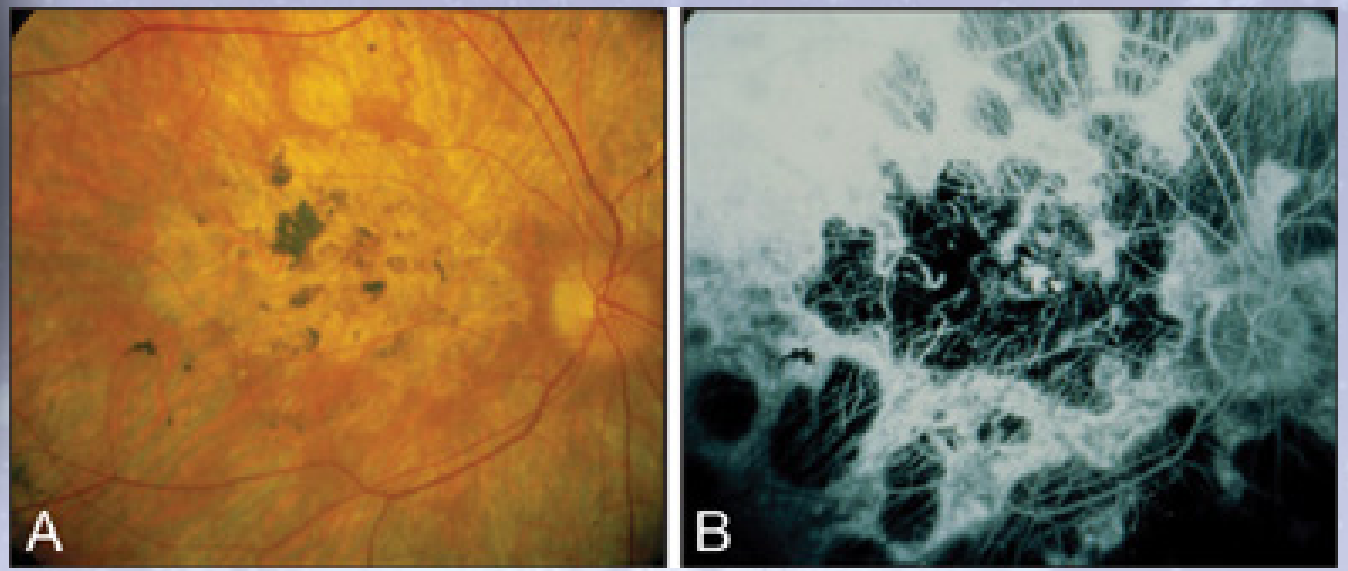
# SYPHILIS



# RUBELLA



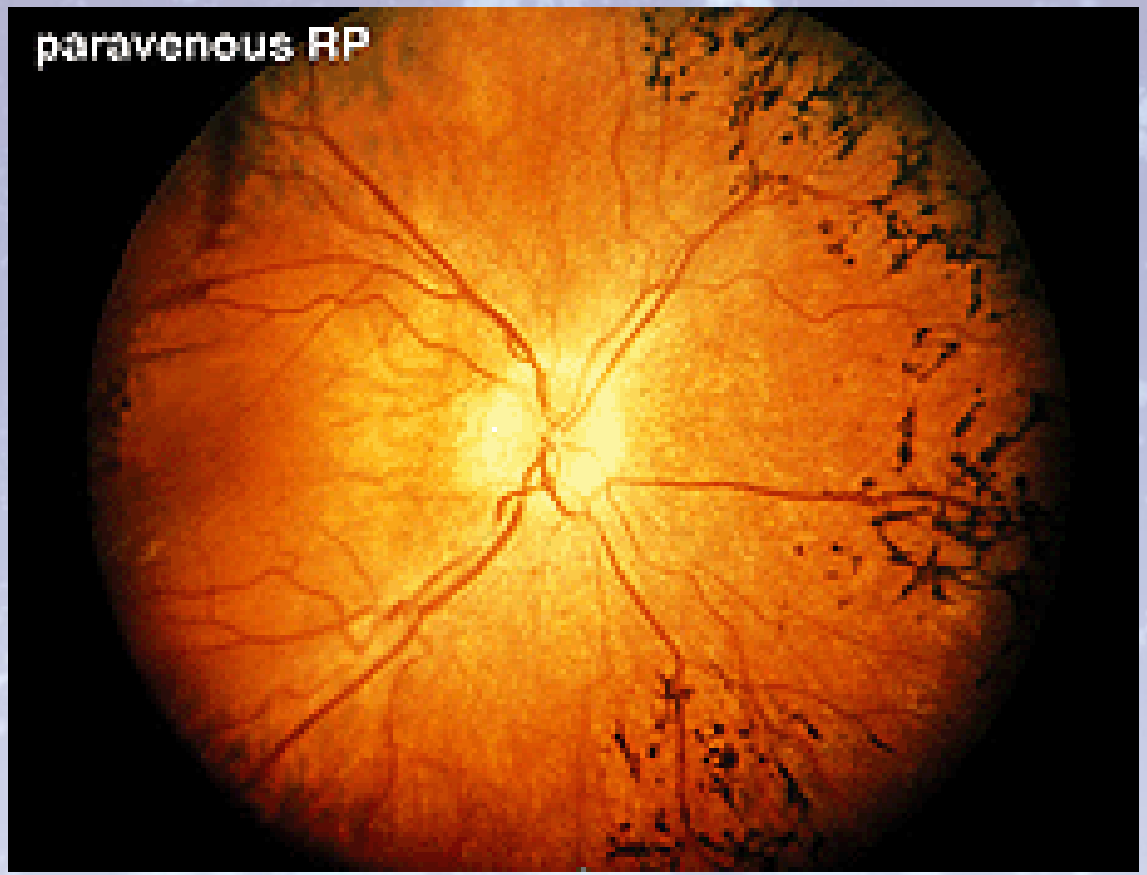
# MELLARIL



# DIFFERENTIAL

- OTHER RETINAL AND CHOROIDAL DYSTROPHIES

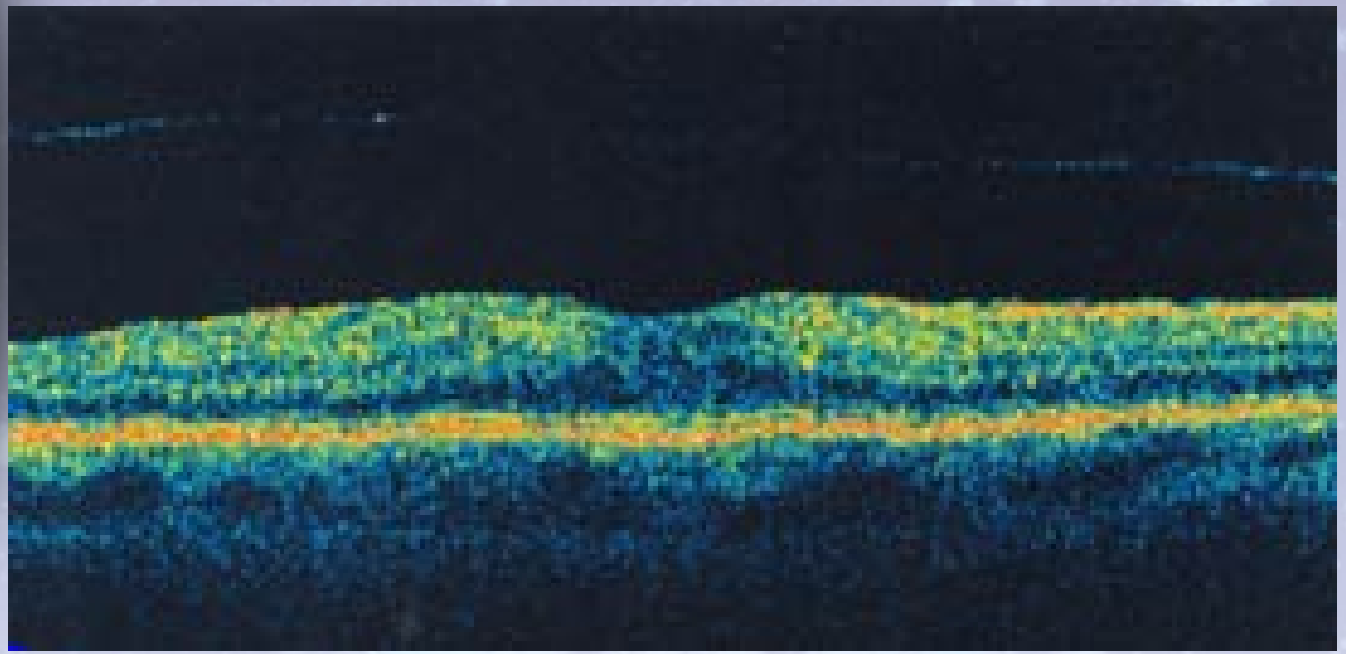
# PIGMENTED PARAVENOUS ATROPHY



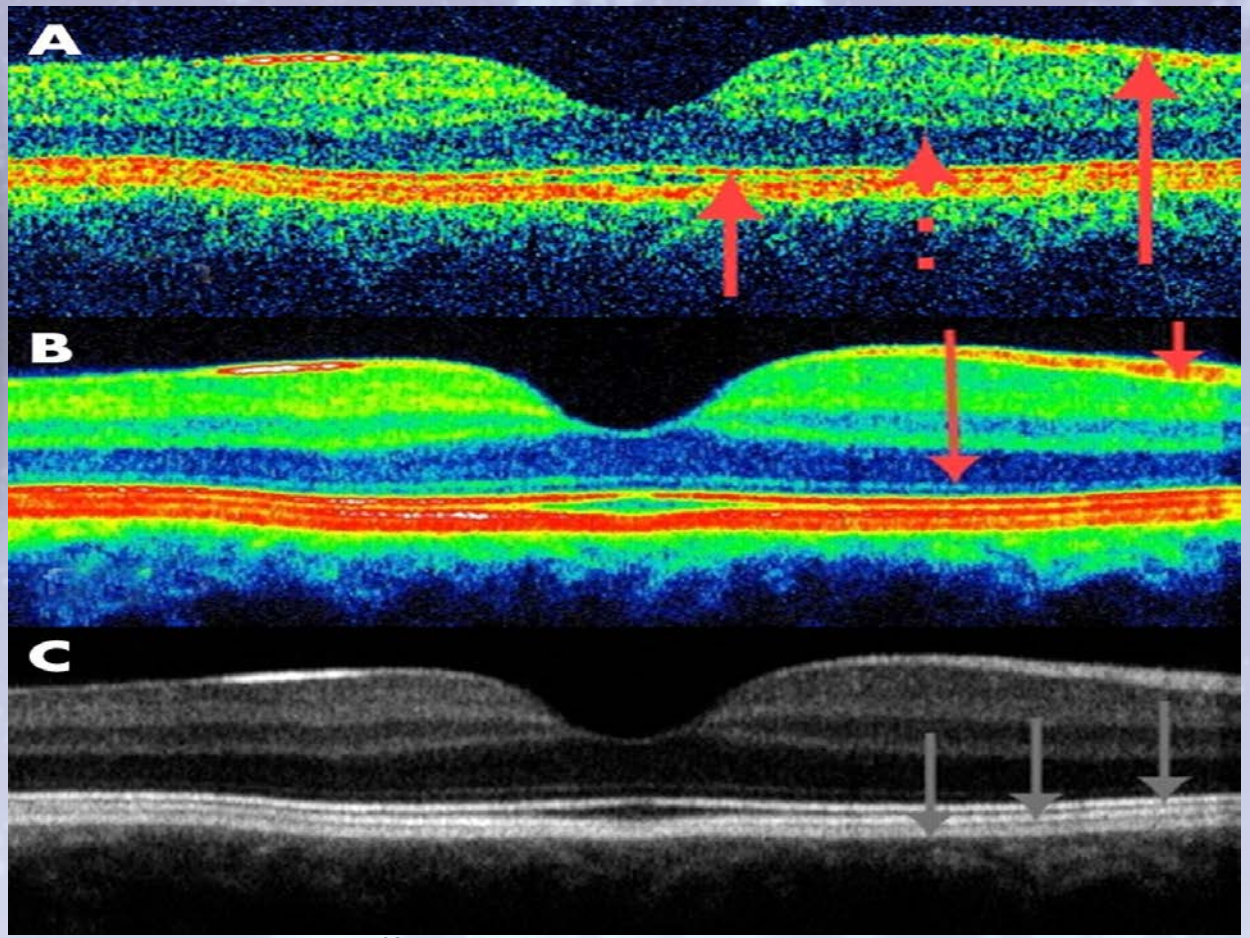
# DIAGNOSTIC TESTS

- COLOR VISION - PARALLELS CONE HEALTH. BLUE - YELLOW MOST COMMON
- FA - CME AND DEGREE OF ATROPHY
- OCT - CME AND RETINAL THICKNESS AS WELL AS RETINAL ANATOMY WITH SDOCT

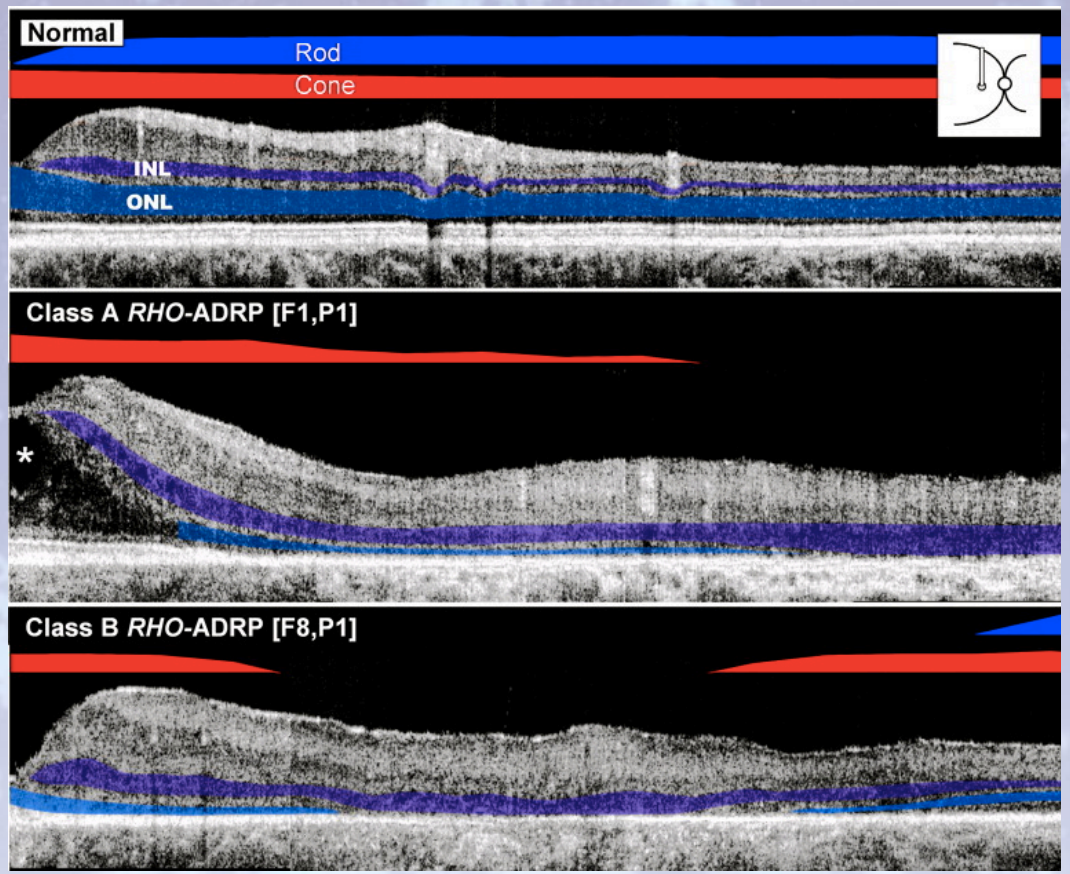
# OCT



# OCT



# OCT IN RETINITIS PIGMENTOSA



# DIAGNOSTIC TESTS

- DARK ADAPTATION - EARLIEST DEFECT EXCEPT FOR ERG
- NOT ALWAYS AVAILABLE. I ALWAYS USED A SIMPLE TEST THAT YOU CAN DO IN YOUR OFFICE AND TAKES ONLY A FEW MINUTES … UNLESS YOU HAVE RP

# DIAGNOSTIC TESTS - ERG

- ERG ABNORMALITY IS REQUIRED TO MAKE THE DIAGNOSIS

- WILL BE ABNORMAL LONG BEFORE CLINICAL SYMPTOMS OR FINDINGS OCCUR

# ERG IN RP

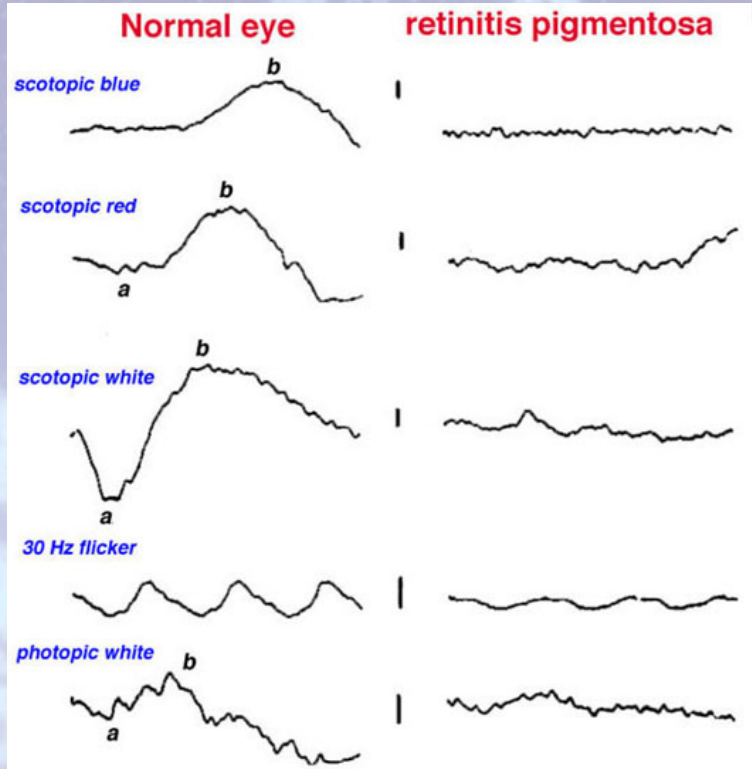



*Fig. 13. ERG recordings in a normal patient and one with retinitis pigmentosa.*

# ERG FINDING IS RP

- DECREASED AMPLITUDE OF SCOTOPIC B WAVE
- IMPLICIT AND LATENT TIMES VARY IN FAMILIES
- PHOTOPIC NORMAL IN EARLY CASES. ABNORMAL LATE

# ERG FINDINGS IN RP

- TWO TYPES OF ERG; SINGLE FLASH AND MULTI FOCAL
- CONVENTIONAL ERG IS A MASS RESPONSE. FOCAL ERG WILL MEASURE AT SET DEGREES

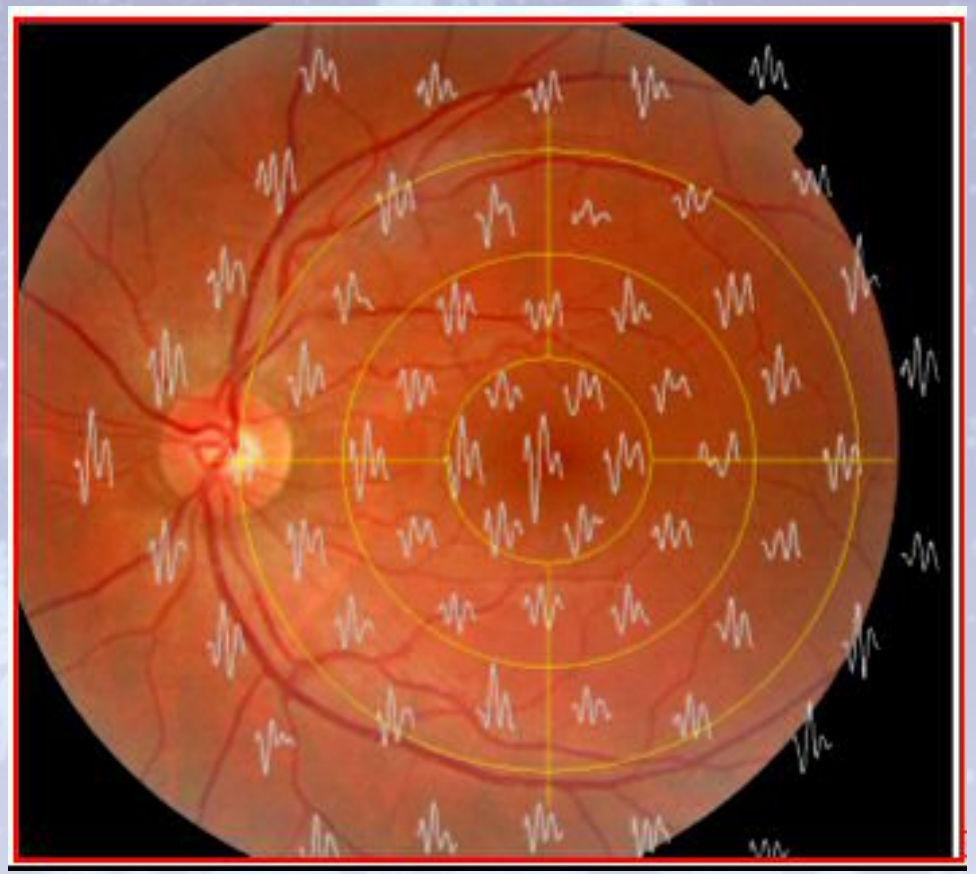
# ERG FINDINGS IN RP

- MULTI FOCAL ERG CAN PROVIDE A HIGH RESOLUTION MAPPING OF THE POSTERIOR POLE

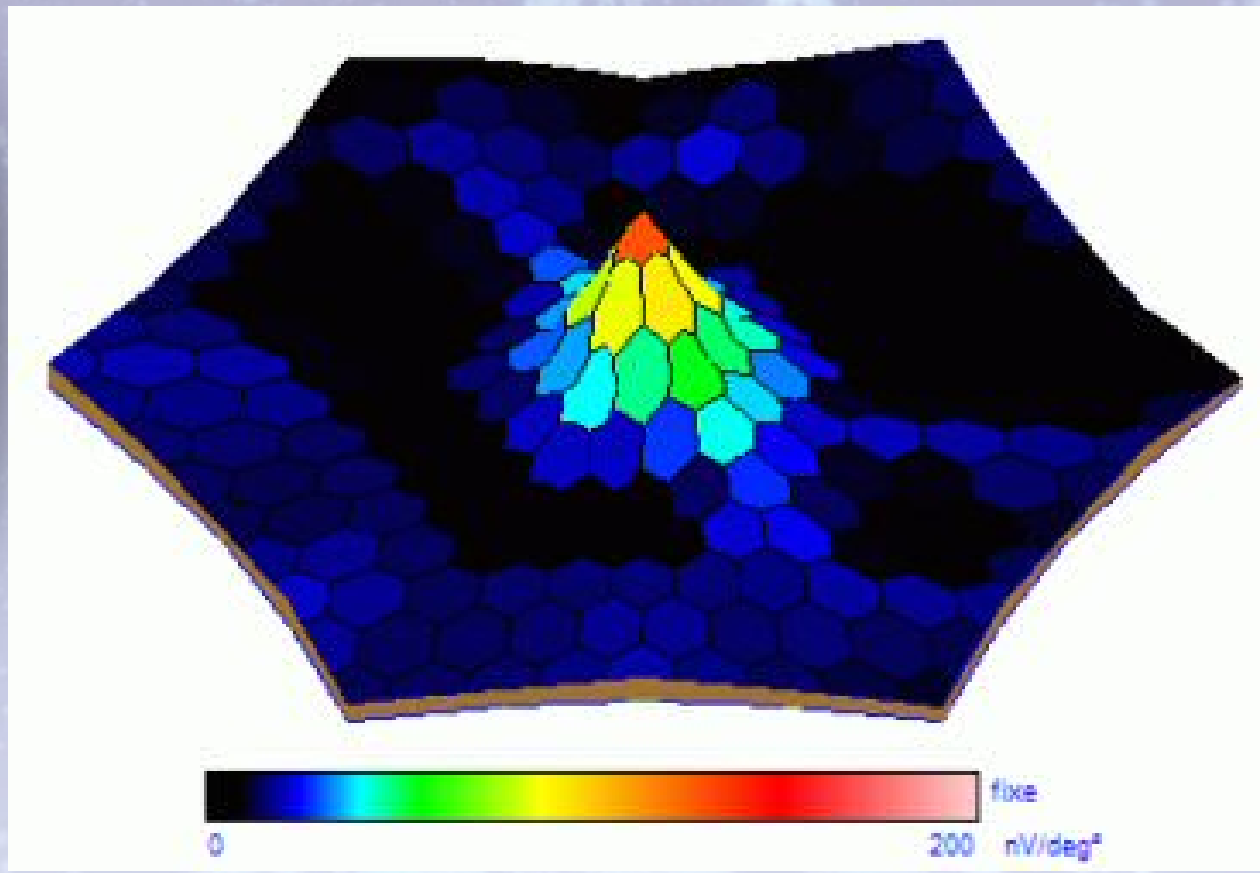
- IN MULTIFOCAL ERG IMPLICIT TIME IS MORE MORE SENSITIVE A PREDICTOR THEN AMPLITUDE

# MULTI FOCAL ERG

# MULTI FOCAL ERG



# MULTI FOCAL ERG



# EOG

- NOT AS RELIABLE IN RETINITIS PIGMENTOSA AS THE ERG
- USEFUL IN DIAGNOSING THE CARRIER STATE OF X LINKED RETINITIS PIGMENTOSA

# VISUAL FIELD DEFECTS

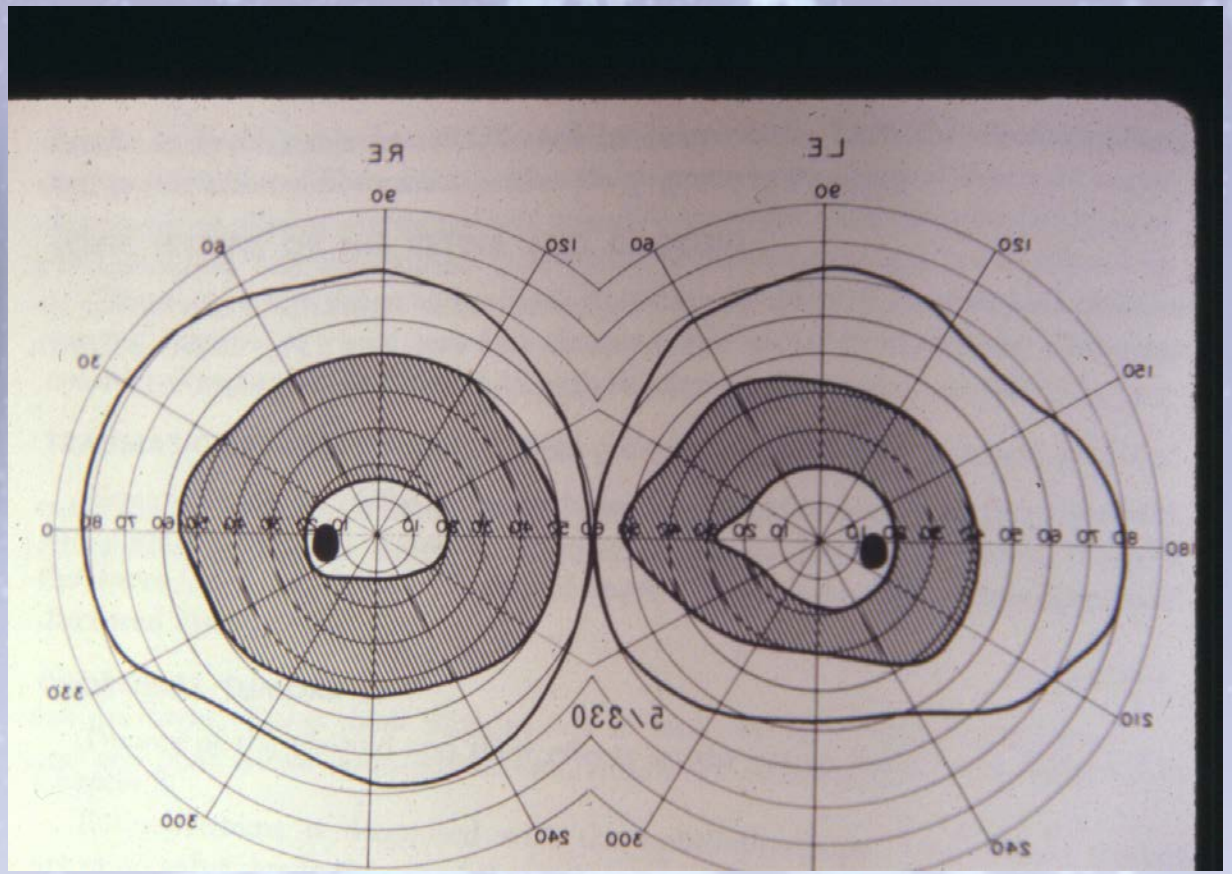
- MOST COMMON IS RING OR ANNULAR FIELD LOSS
- WILL VARY DEPENDING ON TYPE OF RP AND HEREDITARY PATTERN
- USUALLY START IN INFERIOR TEMPORAL QUADRANT

# VISUAL FIELD DEFECT

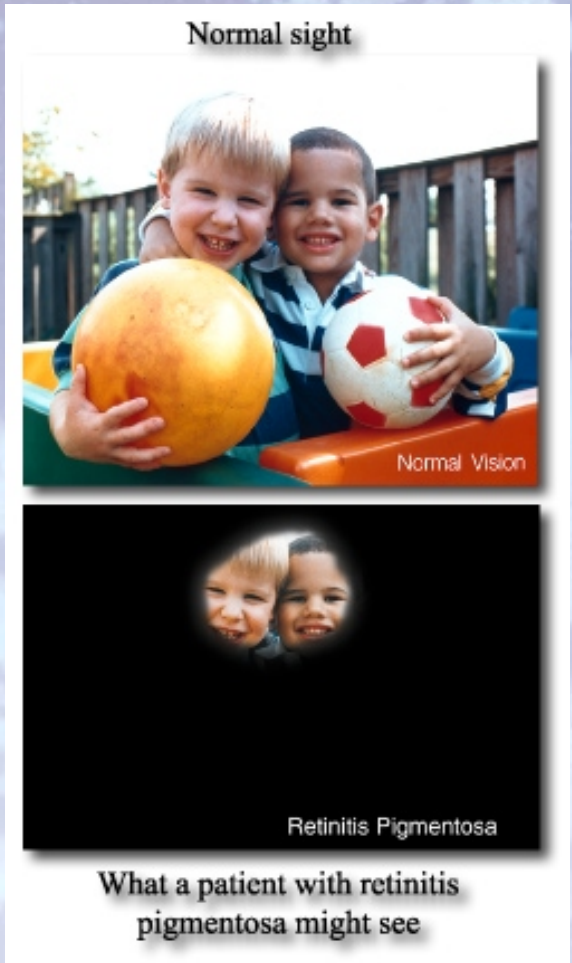
- RING SCOTOMA USUALLY BETWEEN THE 10 - 40 MERIDIAN. CAN HAVE DOUBLE RING WHICH JOIN OVER TIME

- ADVANCED CASES 5 - 10 DEGREES " GUN BARREL" AND SMALL ISLAND INFRO TEMP

# VISUAL FIELD IN RP



# VISUAL FIELD IN RP



# DNA TESTING

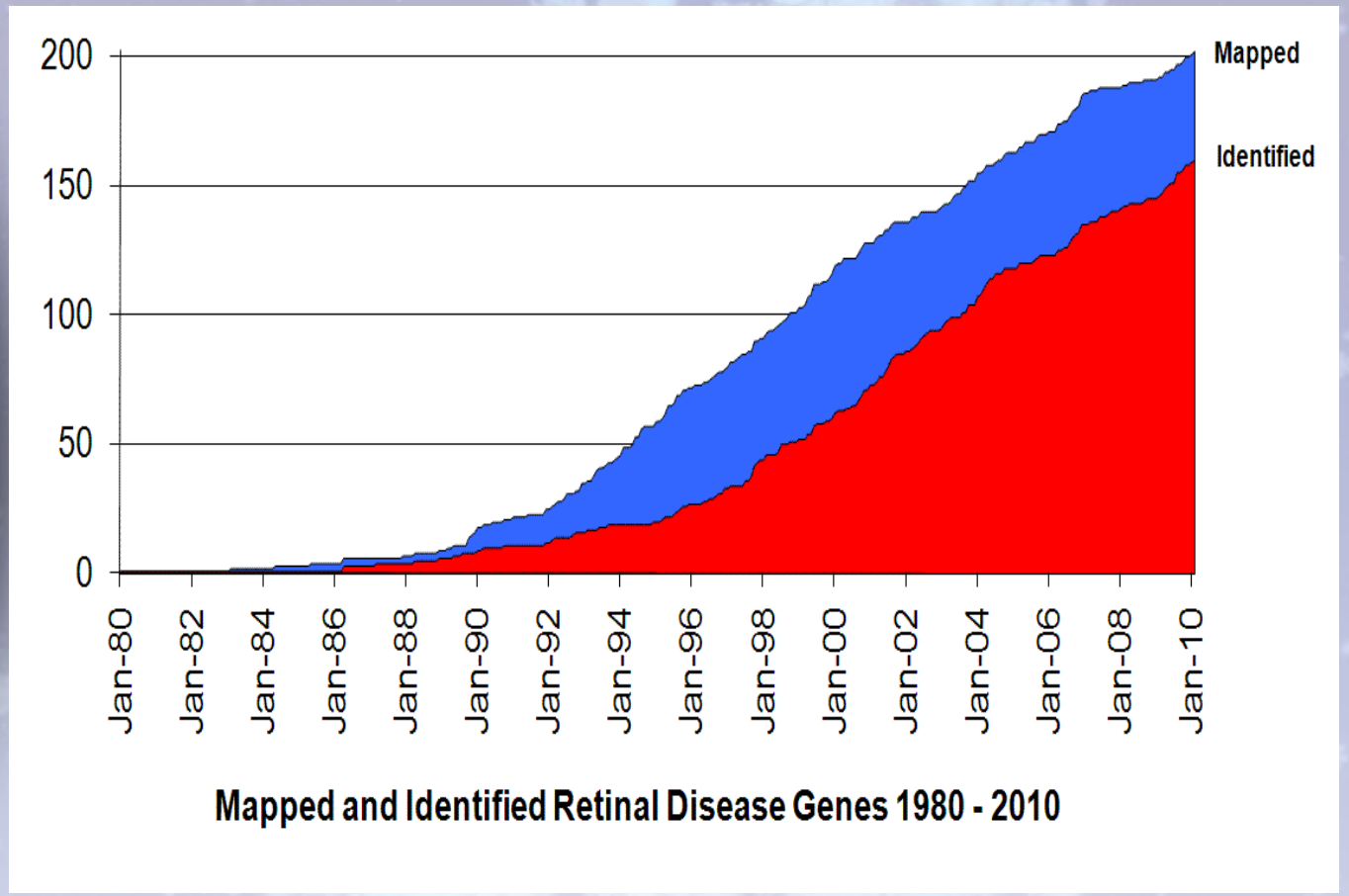
- 29 laboratories in the United States. 6 in California.
- 30 laboratories world wide.
- In addition there are numerous research centers that perform DNA testing.

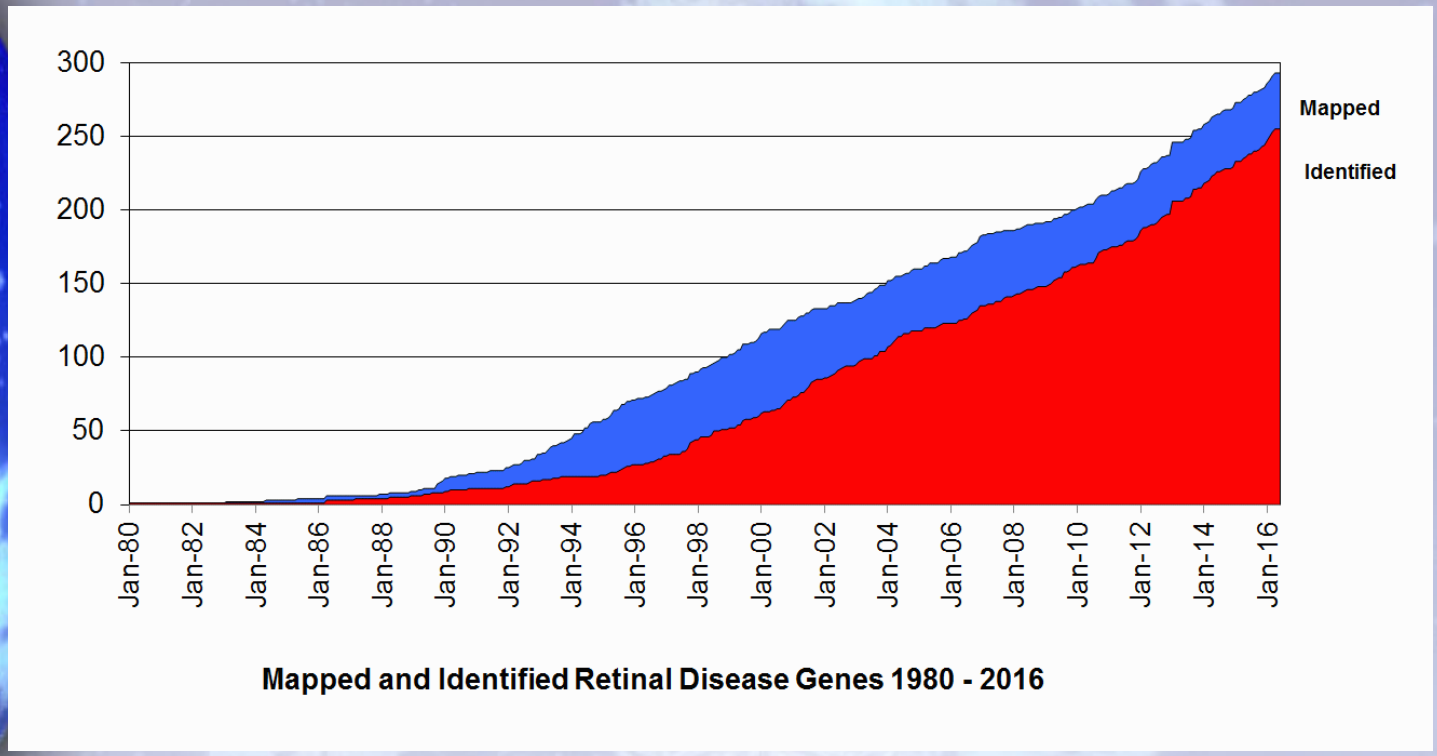
# DNA TESTING

- 293 retinal diseases have been mapped.
- 256 identified at DNA level
- Total number of gene loci dominant RP 23 Identified genes 22. Recessive 39 loci 36 genes.

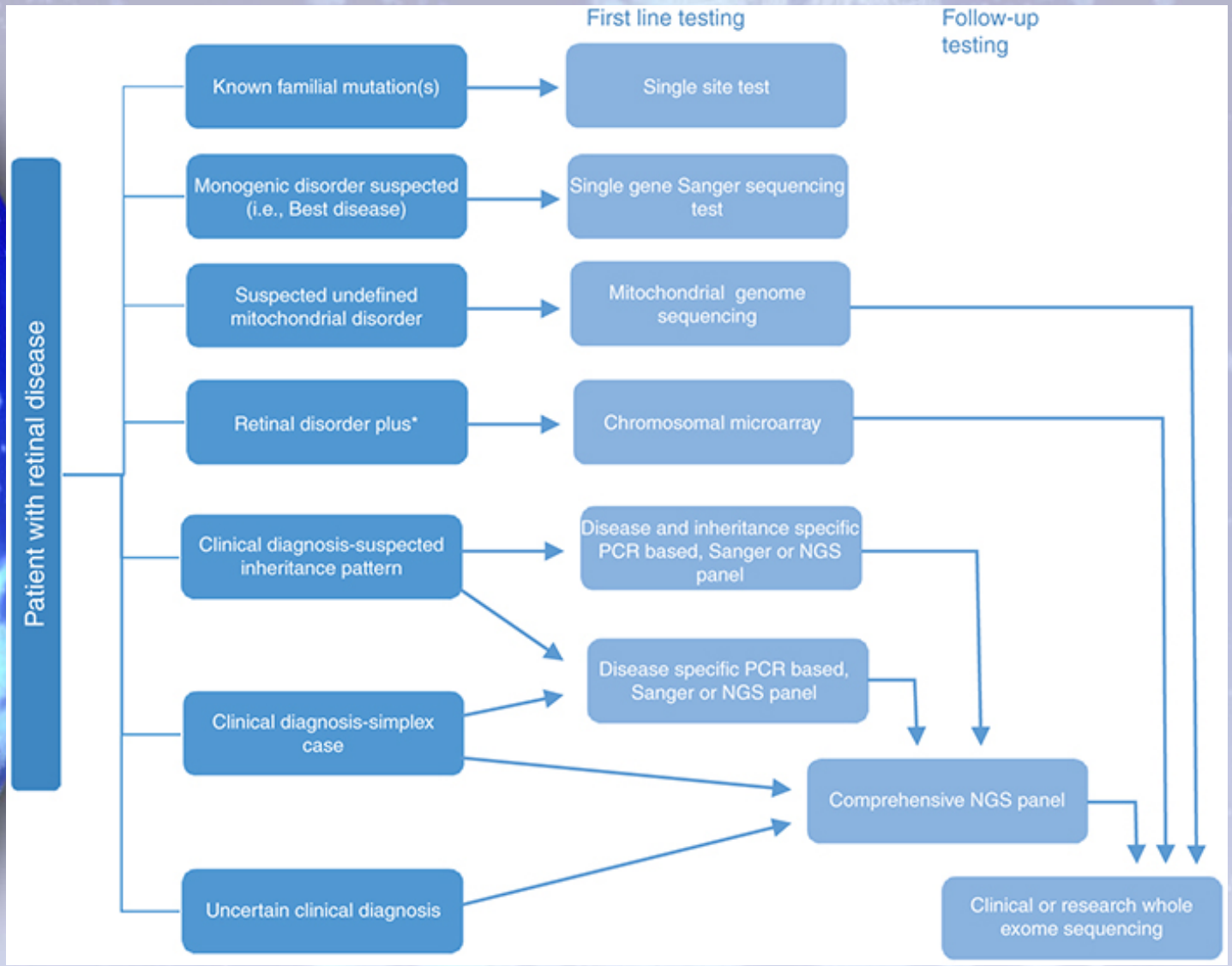
# DNA TESTING

- X Linked RP 5 gene loci. 1 gene.
- Leber Congenital Amaurosis autosomal dominant 1 gene loci. 1 gene. Recessive 12 gene loci. 12 genes.


200
150
100
50
0
Mapped
Identified
Jan-80
Jan-82
Jan-84
Jan-86
Jan-88
Jan-90
Jan-92
Jan-94
Jan-96
Jan-98
Jan-00
Jan-02
Jan-04
Jan-06
Jan-08
Jan-10
Mapped and Identified Retinal Disease Genes 1980 - 2010




**Mapped and Identified Retinal Disease Genes 1980 - 2016**


First line testing
Follow-up testing
Patient with retinal disease
Known familial mutation(s)
Single site test
Monogenic disorder suspected (i.e., Best disease)
Single gene Sanger sequencing test
Suspected undefined mitochondrial disorder
Mitochondrial genome sequencing
Retinal disorder plus*
Chromosomal microarray
Clinical diagnosis-suspected inheritance pattern
Disease and inheritance specific PCR based, Sanger or NGS panel
Disease specific PCR based, Sanger or NGS panel
Clinical diagnosis-simplex case
Comprehensive NGS panel
Uncertain clinical diagnosis
Clinical or research whole exome sequencing

| Type of testing | Indication | Turnaround time (weeks) | Approximate cost[a] |
|---|---|---|---|
| Single site testing | • Familial mutation(s) is known | 2–3 | $120–500 |
| Sanger sequencing | • Clinical diagnosis of a monogenic disorder | 3–6 | $200–2,000[b] |
| Chromosomal SNP microarray | • Clinical suspicion of syndromic retinopathy | 1–4 | $2,500 |
| Mitochondrial genome sequencing | • Clinical suspicion of an unknown mitochondrial syndrome | 7–8 | ~$3,000 |
| Disease-specific Sanger sequencing or NGS gene panels | • Clinical diagnosis of a heterogeneous disorder | 6–12 | $300–4,000[c] |
| Array CGH deletion/duplication panels | • Clinical diagnosis of a heterogeneous disorder<br>• Ordered in conjunction with or after negative (or only one AR variant) NGS panels | 2–4 | $650–1,300 |
| Comprehensive NGS retina gene panels | • Clinical diagnosis of a heterogeneous disorder<br>• Uncertain diagnosis | 12 | ~$2,500 |
| Whole-exome sequencing | • Clinical diagnosis of a heterogeneous disorder<br>• Uncertain diagnosis<br>• Negative findings on previous NGS | 12–24 | $5,000–7,000[d] |

AR, autosomal recessive; CGH, comparative genomic hybridization; NGS, next-generation sequencing; SNP, single-nucleotide polymorphism.

[a]The "approximate cost" was derived by surveying four to seven laboratories offering each specific test to provide a frame of reference. Clinicians should consult laboratory personnel or websites for up-to-date pricing. [b]Price variation largely reflects the number of exons required to sequence. [c]Price variation largely reflects the number of genes analyzed in a Sanger sequencing or NGS panel. [d]Price estimations are for proband-only testing.

# CLINICAL COURSE

- ONSET USUALLY IN TEENS BUT ERG FINDINGS ARE PRESENT MUCH EARLIER THEN SYMPTOMS OF CLINICAL CHANGES.

# CLINICAL COURSE

- FIRST SYMPTOM IS OFTEN NYCTALOPIA OR FIELD DEFECT
- IN SOME CASES DIAGNOSIS NOT MADE UNTIL CATARACT, MACULAR , OR CONE INVOLVEMENT

# CLINICAL COURSE

- PROGRESSION DEPENDS ON MODE OF TRANSMISSION
- DOMINANT MOST BENIGN WITH VA 20/30 - 100 UNTIL 5TH AND 6TH DECADE
- RECESSIVE, ISOLATED AND X - LINKED MOST SEVERE

# CLINICAL COURSE

- FISHMAN REPORTED THAT ALL HIS X - LINKED OVER 30 HAD 20/80 OR LESS. RECESSIVE HAD SIMILIAR RESULTS

- TOTAL BLINDNESS IN THESE MODES COMMON BUT SOME DO RETAIN VA INTO SIXTIES

# CLINICAL COURSE

- CHECK THE FAMILY. THAT WILL OFTEN TELL MORE ABOUT THE PROGESSION FOR A PARTICULAR INDIVIDUAL
- GOOD FAMILY HISTORY IMPORTANT. PATIENTS HAVE TO MAKE THE CALL TO RELATIVES

# Treatment

- VITAMIN A SUPPLEMENTATION
- DOCOSAHEXAENOIC ACID – DHA
- LUTEIN
- GANGLIOSIDES
- BETA-CAROTENE ACID
- ORAL VALPROIC ACID
- CILIARY NEUROTROPHIC FACTOR-CNTF
- HYPERBARIC OXYGEN

# TREATMENT

- IN 1993 BERSON ET AL REPORTED THAT TREATMENT WITH 15000 IU OF VITAMIN A PALMINTATE SLOWED THE PROGRESSON OF CONE ERG

# TREATMENT

- NEI CONFIRMED VALUE OF VITAMIN A IN RP BUT CAUTIONED USE IN OTHER HEREDITARY DISEASES AS IT CAUSES ACCELERATED INCREASE IN LIPOFUCSIN.
- FISH OIL HAS SHOWN BENEFIT. AFFECTS RATE OF DECLINE OF ERG AMPLITUDES.

# TREATMENT OF CME IN RETINITIS PIGMENTOSA

- CARBONIC ANHYDRASE INHIBITORS
- DIAMOX
- METHAZOLAMIDE
- DORZOLAMIDE

# TREATMENT OF CME IN RETINITIS PIGMENTOSA

- DIAMOX HAS BEEN SHOWN IN SEVERAL STUDIES TO BE EFFECTIVE IN REDUCING MACULAR EDEMA AND RETINAL THICKNESS. VISUAL RESULTS ARE VARIABLE .

# TREATMENT OF CME

- SIDE EFFECTS ARE COMMON AND REBOUND OCCURS IN OVER 30%
- METHAZOLMIDE NOT AS EFFECTIVE
- DORZOLAMIDE DROPS

# TREATMENT OF CME

- DORZOLAMIDE DROPS REDUCES THICKNESS WITH VARIABLE VA RESULTS. REBOUND IN 31%
- STUDIES COMPARING DROPS TO ORAL INDICATE ORAL MORE EFFECTIVE

# TREATMENT OF CME

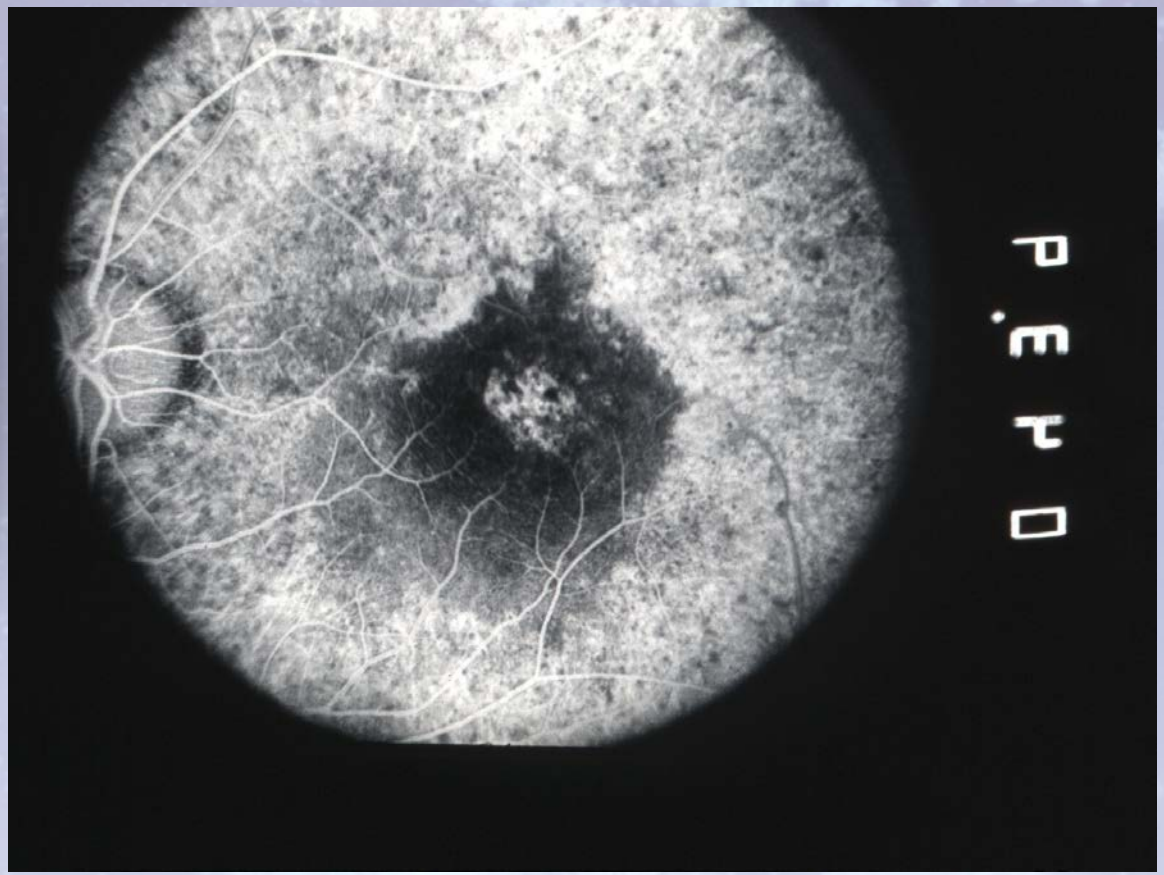
- INTRAVITREAL KENALOG HAS HAD BETTER ANATOMIC THEN VISUAL RESULTS. SEVERAL RISK FACTORS

- IVK CAN BE USED IN COMBINATION THERAPY

# TREATMENT OF CME WITH ANTI VEGF

- ONLY A FEW REPORTED STUDIES AND CASE REPORTS
- 30 PATIENTS WITH 6 MONTH HISTORY OF CME FAILED ON DIAMOX. 15 INJECTED WITH O.5 LUCENTIS. 87% SIGNIFICANT RESOLUTION OF CME AT 6 MONTHS ON SINGLE INJECTION. NO DIFFERENCE IN VISION.

# RETINITIS PIGMENTOSA



ATROPHY IN CENTRAL MACULAR AFTER RESOLUTION OF CME

# TREATMENT OF CME WITH ANTI VEGF

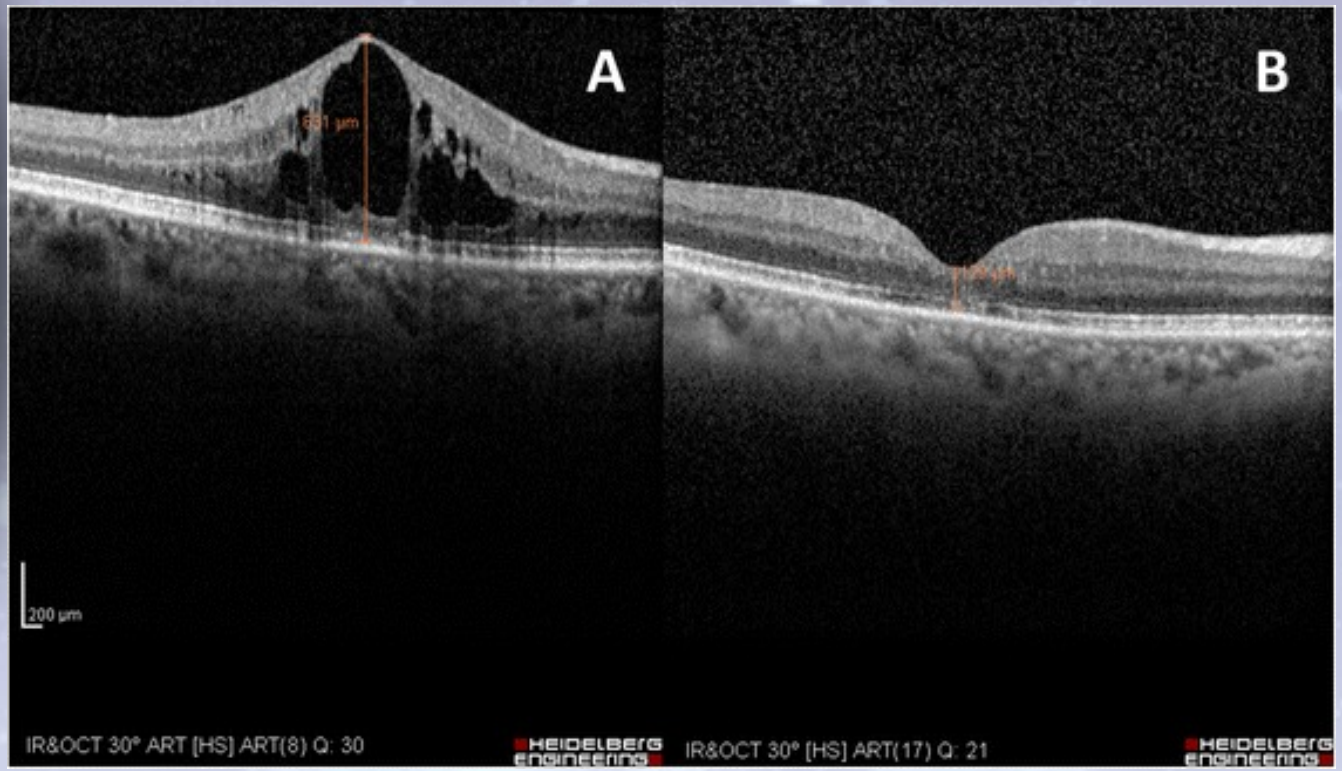
- AVASTIN 1.25 MG IN 13 EYES OF 7 PATIENTS. WAS FOUND TO BE EFFECTIVE IN REDUCING THICKNESS AND IMPROVING VISUAL ACUITY

- 2 CASES BOTH FAILED WITH AVASTIN BUT RESPONDED TO IVK

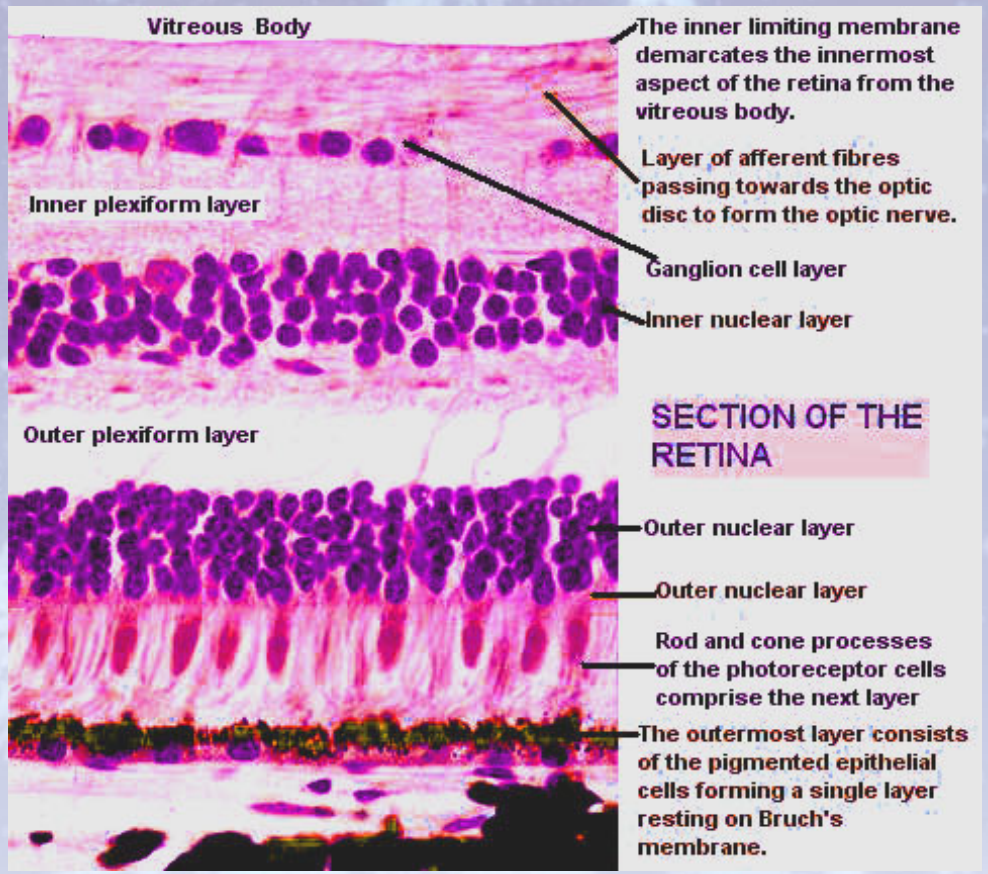
# TREATMENT OF CME WITH ANTI VEGF

- TWO REPORTS OF TREATMENT OF CME SECONDARY TO RP WITH AFIBERCEPT ( EYLEA).
- MOUSTAFA BMC 2015- SINGLE INJECTION OF 0.05ML/0.50MG EYLEA.IMPROVED VISION AND DECREASED THICKNESS LASTED AT 3 AND 6 MONTH EXAMS.

# TREATMENT OF CME WITH ANTI VEGF



# NORMAL RETINA



# NORMAL RETINA

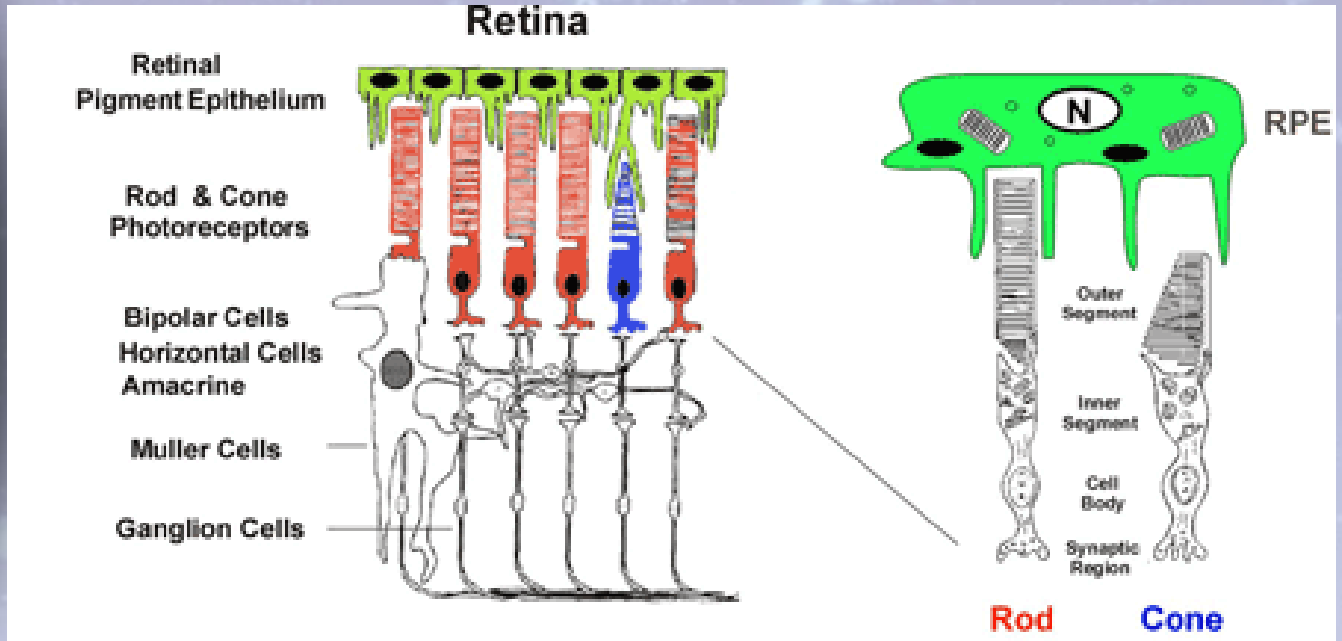



Fig 1. Diagram showing the organization of cells in the retina (left) and the rod and cone photoreceptors cells that lie against the retinal pigment epithelial cells (RPE).

# ON THE HORIZON

- CELLS TAKEN FROM DEVELOPING RETINAS AT THE TIME OF PEAK ROD GENESIS WILL RESULT IN SYNAPTIC CONNECTIONS,INTEGRATION AND IMPROVEMENT OF VISUAL ACUITY

# ON THE HORIZON

- OTANI, ET AL J.CLIN. INVEST 2004 DEMOSTRATED THAT INJECTION OF BONE MARROW DERIVED HEMATOPOIETIC STEM CELLS INTO THE VITREOUS PREVENT CONE LOSS

# ON THE HORIZON

- THE STEM CELLS CONTAIN ENDOTHELIAL PRECURSORS WHICH INCORPORATE INTO VESSELS THAT WOULD DISAPPEAR SECONDARY TO ROD DEATH

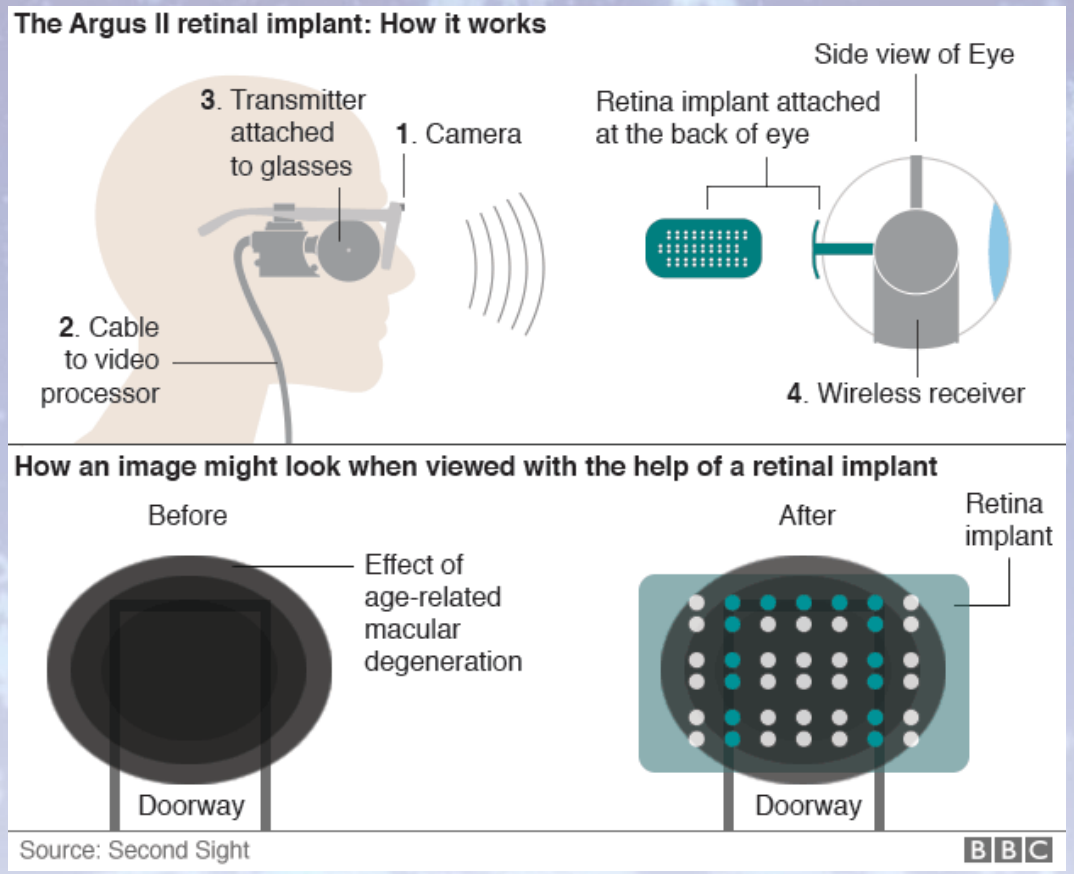
- USING AUTOLOGOUS CELLS PREVENTS REJECTION

# ON THE HORIZON

- GENE THERAPY. 2010 SUN ET AL. REPORTED THAT THEY WERE ABLE TO ACHIEVE RESCUE OF BOTH ROD AND CONES WITH A SINGLE PROMOTER. THIS WAS A FIRST AND CAN LEAD TO HUMAN TRIALS.

# ARGUS II RETINAL PROSTHESIS

# ARGUS II RETINAL PROSTHESIS



# PROGNOSIS

- VARIES SIGNIFICANTLY AMONG INHERITANCE TYPES
- SANDBERG IO 2008 FOUND THAT RECESSIVE ( USH2A)MEAN ANNUAL DECLINE VA 2.6%, VF 7%,ERG13.2%
- FASTER THEN DOM (RHO), SLOWER THEN X-LINKED (RPGR)

# PROGNOSIS

- BERSON EER 2007 STUDIED HOW LONG FOR CONE ERGS TO CHANGE FROM 30HZ TO 0.05MIRCO V ( VIRTUAL BLINDENESS).

- 10% OF CONE ERG PER YEAR NOT ON RX, 8.3% ON RX

# PROGNOSIS

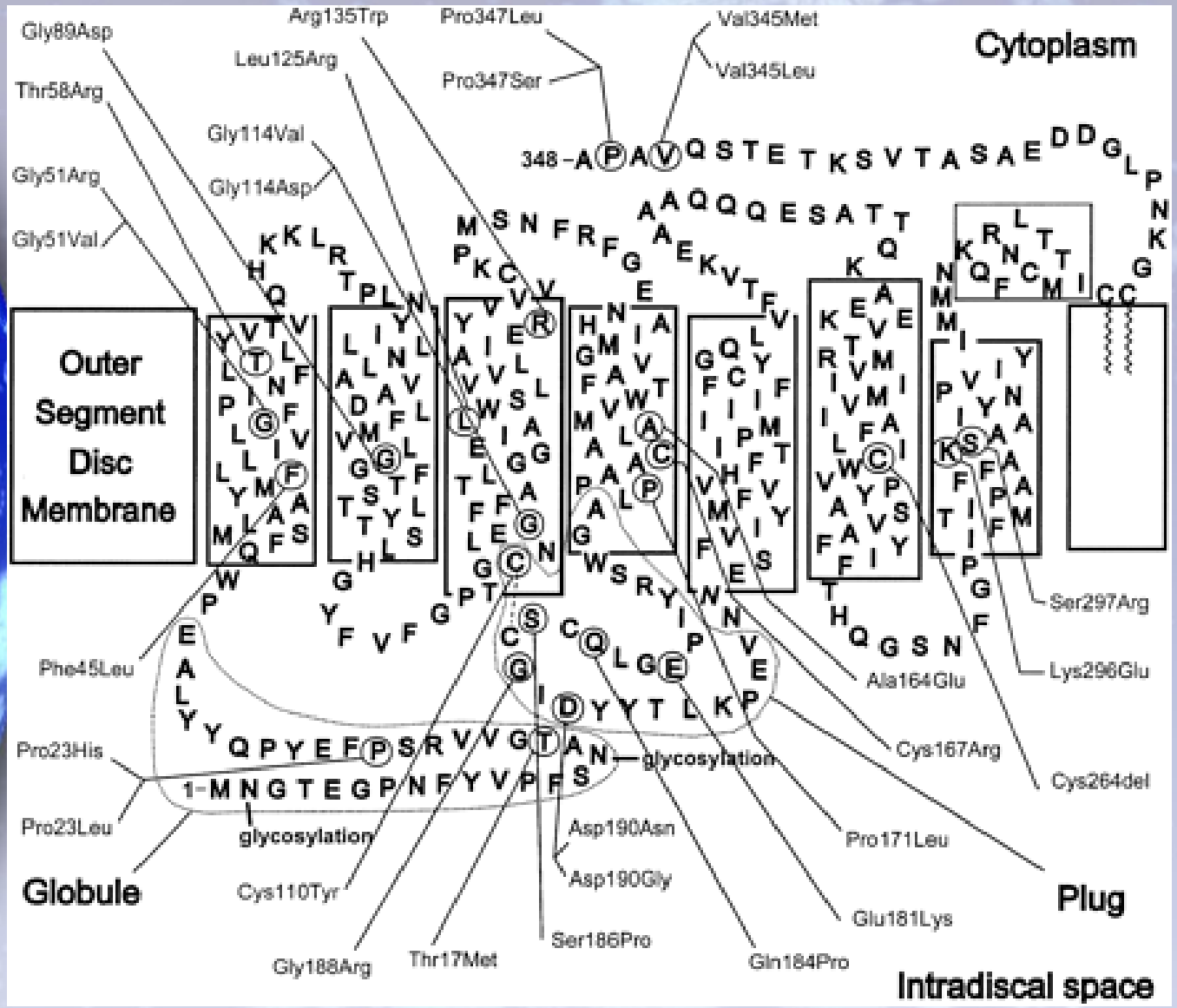
- BERSON - IF PATIENT HAS A 3.5 MICRO V AT AGE 40 (25% OF RP PATIENTS) PATIENT WOULD BE EXPECTED TO RETAIN SOME USEFUL VA FOR THEIR ENTIRE LIFE WITHOUT RX

# PROGNOSIS

- BERSON INVES OPHTH 2002 STUDIED THE PROGRESSION IN THE DOMINANT FORM OF RP WITH RHODOPSIN MUTATIONS
- 20 - 25 % OF DOMINANT HAVE THESE MUTATIONS
- 100 DIFFERENT MUTATIONS PRESENT

# PROGNOSIS

- 3 MAIN TYPES OF RHODOPSIN MUTATIONS FOUND
- GLOBULE 39% , PLUG 14%, AND C-TERMINAL 20%
- RATE OF VA LOSS DID NOT VARY AMONG GROUPS


Cytoplasm
Outer Segment Disc Membrane
Globule
Plug
Intradiscal space
Gly89Asp
Thr58Arg
Gly51Arg
Gly51Val
Arg135Trp
Leu125Arg
Gly114Val
Gly114Asp
Pro347Leu
Pro347Ser
Val345Met
Val345Leu
Phe45Leu
Pro23His
Pro23Leu
glycosylation
glycosylation
Cys110Tyr
Gly188Arg
Thr17Met
Asp190Asn
Asp190Gly
Ser186Pro
Gln184Pro
Glu181Lys
Pro171Leu
Ala164Glu
Cys167Arg
Lys296Glu
Ser297Arg
Cys264del

# PROGNOSIS

- FIELD LOSS AND ERG DECLINE WAS GREATEST FOR C-TERMINAL AND LEAST FOR PLUG

- MEAN ANNUAL DECLINE WAS 1.86% VA, 2.65% VF, 8.7% ERG

# SYNDROMES

- DEAFNESS MAY OCCUR IN UP TO 40% OF ALL CASES OF RP

- THIS IS BELIEVED TO BE BASED ON SIMILAR EMBRYOLOGICAL ORIGIN OF THE RPE AND THE EPITHELIUM OF THE ORGAN OF CORTI

# USHER'S SYNDROME

- LEADING CAUSE OF DEAFNESS AND BLINDNESS WORLDWIDE
- 20,000 CASES IN US
- 3 - 6% OF ALL DEAF AND HARD OF HEARING CHILDREN

# USHER'S SYNDROME

- 9 GENES ISOLATED
- 3 TYPES OF USHER'S
- 95% ARE TYPES 1 AND 2
- AUTOSOMAL RECESSIVE
-

# USHER'S SYNDROME

- TYPE 1 - PROFOUND HEARING LOSS , RP , BALANCE PROBLEMS. 5 GENES

- TYPE 2 - MOD - SEVERE HEARING LOSS , RP , NO BALANCE PROBLEMS.3 GENES

- TYPE 3 - PROGRESSIVE HEARING LOSS,RP , + - . 1 GENE

# OTHER SYNDROMES

- HALLGREN'S
- REFSUM'S
- COCKAYNE'S
- ALSTROM'S
- DIALINAS - AMALRIC
- LAWRENCE-MOON-BARDET-BIEDL

# LEBER'S CONGENITAL AMAUROSIS ( LCA)

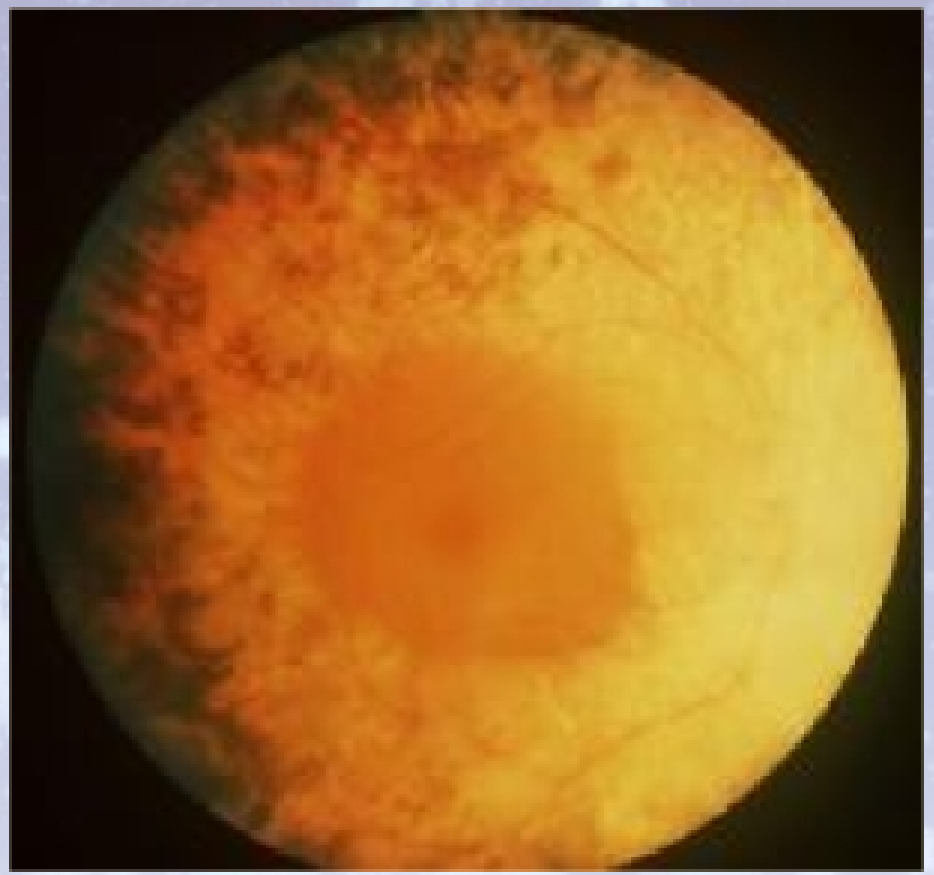
- LCA IS NOT UNCOMMON. 2 -3 / 100,000. 18% OF CONGENITALLY BLIND IN HOLLAND, 10% IN SWEDEN

- AUTOSOMAL RECESSIVE.

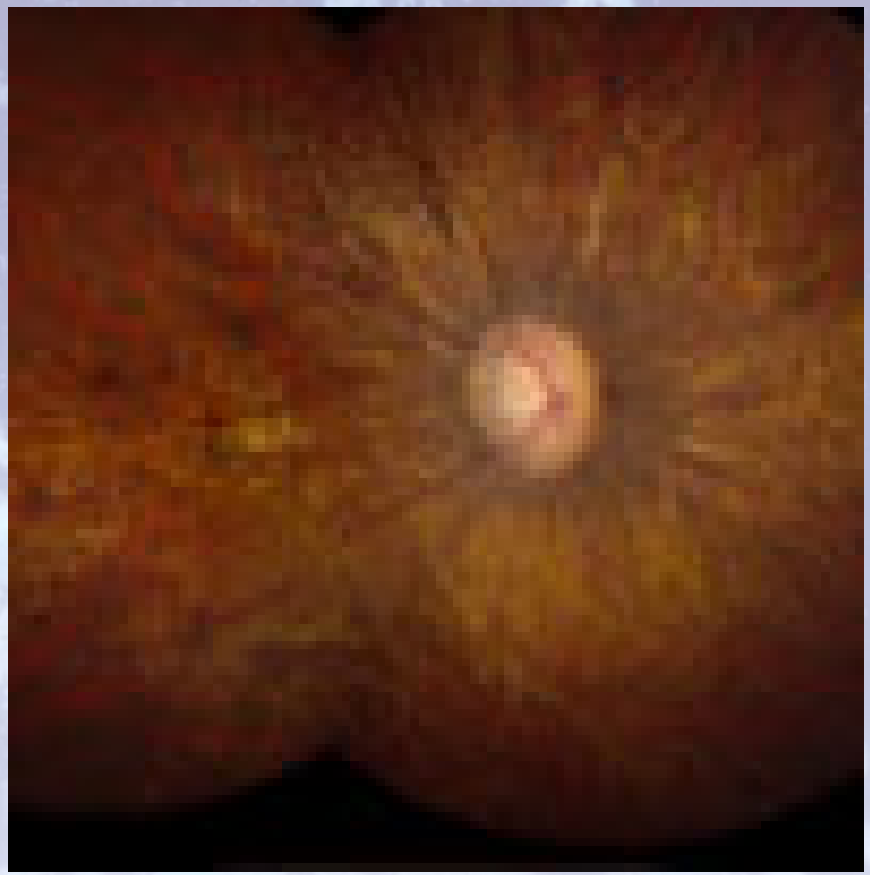
# LCA

- DECREASED VISION AT BIRTH OR WITHIN FIRST YEAR
- NYSTAGMUS COMMON
- PHOTOPHOBIA
- MINIMALLY REACTIVE PUPILS
- VARIABLE PIGMENTARY CHANGES IN RETINA,OPTIC PALLOR,VESSEL ATTENUATION

# LCA



# LCA



# LCA

- NOBLE AND CARR REPORTED THAT 95% OF THEIR PATIENTS HAD VA OF 20/200 OR LESS WITH THE MAJORITY HM TO CF

# GENE THERAPY FOR LCA

- 1997 - NEI INVESTIGATION FOUND THAT MUTATION IN RPE65 GENE CAUSED LCA TYPE OF VISUAL LOSS IN DOGS

- 2000 - DOGS WERE INJECTED WITH SINGLE DOSE OF GENE TRANSFER THERAPY

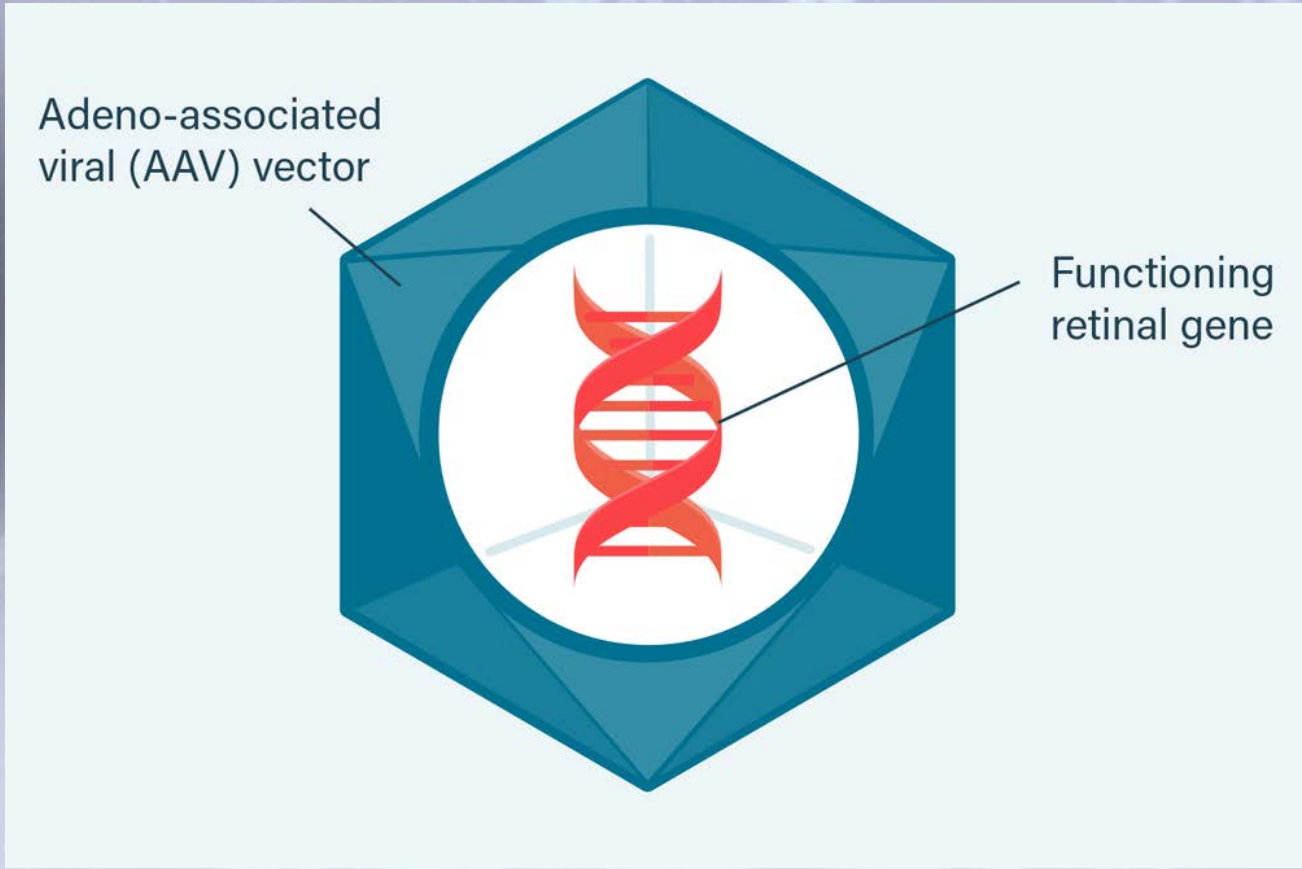
# GENE THERAPY FOR LCA

- INJECTION CONSISTED OF COPIES OF RPE65
- DOGS HAD SIGNIFICANT IMPROVEMENT OF VA AND NYSTAGMUS WAS CORRECTED

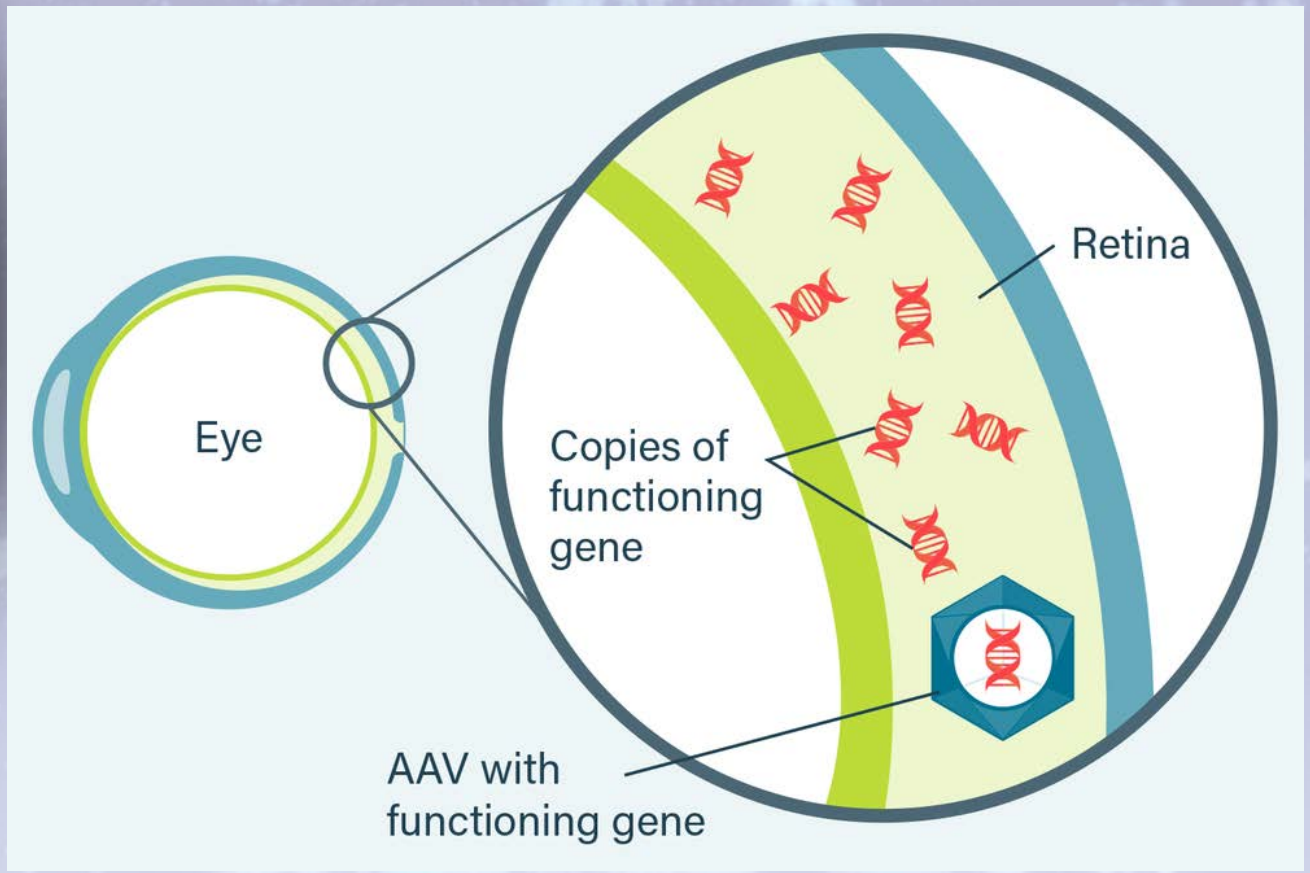
# AAV

- LACK OF PATHOGENICITY
- MIMIMAL IMMUNOGENICITY
- MAINTAIN HIGH LEVELS OF TRANGENE EXPRESSION IN RPE , PHOTORECEPTORS , GANGLION CELLS FOR LONG PERIODS WITH A SINGLE INJECTION

# GENE THERAPY FOR LCA



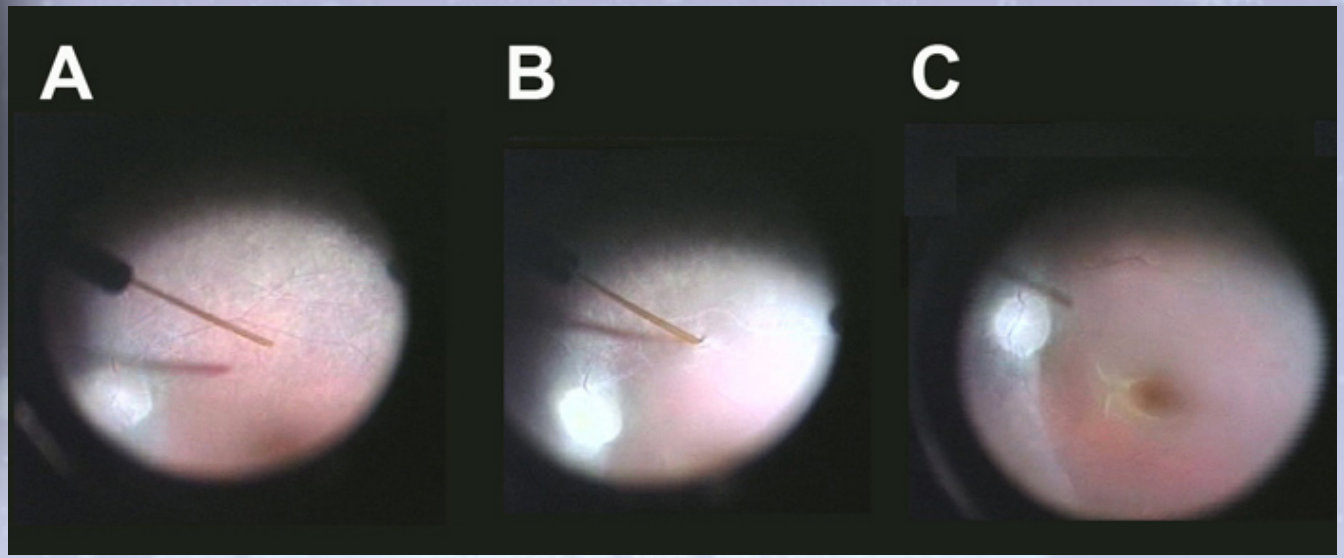
# GENE THERAPY FOR LCA



# GENE THERAPY FOR LCA

- PHASE 1 CLINICAL TRIAL IN 2008. 3 PATIENTS AGES 22,24, 25 INJECTED SUBRETINALLY WITH AAV-RPE65.
- OVER 90 DAYS THERE WAS A 50 FOLD INCREASE IN DAY VA AND 63000 FOLD IN NIGHT VA IN INJECTED AREAS

# GENE THERAPY FOR LCA



# GENE THERAPY FOR LCA

- NO ADVERSE LONG TERM COMPLICATIONS
- AT ONE YEAR THE VA HAD NOT CHANGED BUT ALL 3 COULD SEE VERY DIM LIGHTS AND ONE COULD READ AN ILLUMINATED CLOCK WITH ECCENTRIC FIXATION

# GENE THERAPY FOR LCA

- NEI SPENT $124 MILLION BETWEEN 1993 - 2007 FOR THE BASIC RESEARCH AND $3.7 MILLION ON THE CLINICAL TRIAL

- ONLY TYPE 2 LCA HAS THE RPE65 GENE AND IS ONLY 6% OF CASES OF LCA

ObamaCARE's

# GOLD FOR GRANDPA

Program

**TRADE-IN OLD, HIGH MAINTENANCE GRANDPARENTS**

**FOR CA$H PRIZES AND FREE HEALTHCARE CREDITS!**

*How much is your old family member worth?*

*Take them to the nearest government*

**Planned Obsolecence Center**

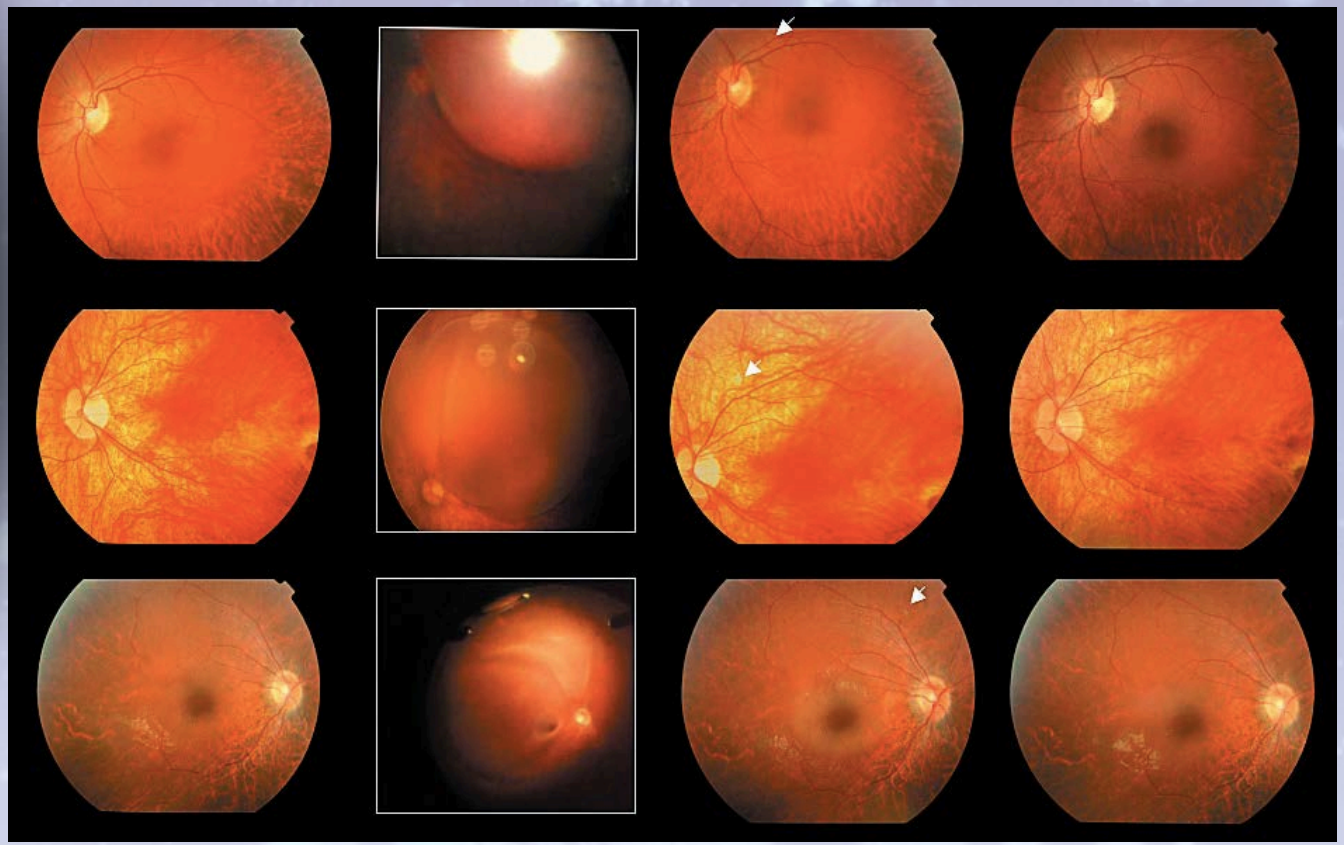
*for a free estimate today!*

*Modeled after the Cash For Clunkers program,*
*you too can trade-in your old "clunker" of a grandparent*
*for FREE Taxpayer Money!*
*Maximum four grandparents per family.*
*Must be over 65 years of age. Limitations may apply.*
*Old grandparents will be destroyed to save the planet.*

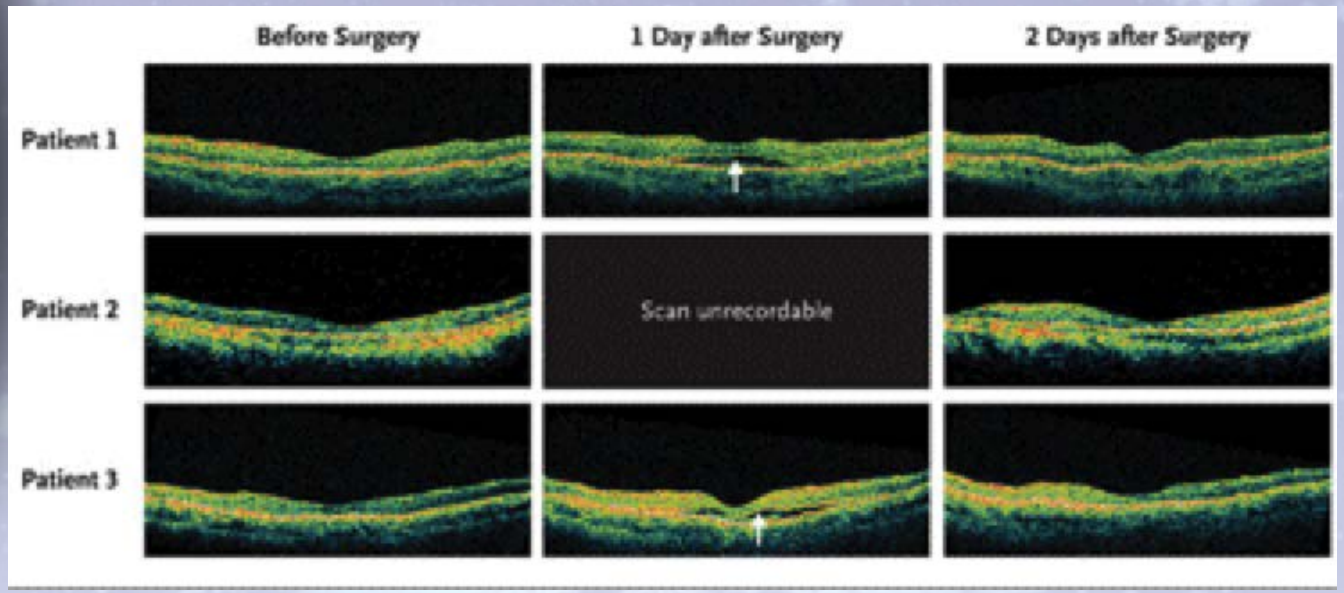
# GENE THERAPY FOR LCA

- LANCET 2009 MAGUIRE ET AL
- 12 PATIENTS GIVEN RPE65 . AGE RANGE 8 -44. 2 YEAR FOLLOW UP. STUDY LOOKED AT AGE AND DOSE.
- ALL HAD IMPROVEMENT IN VF AND PUPILLARY RESPONSE

# LCA



# GENE THERAPY FOR LCA



# GENE THERAPY FOR LCA

- NEJM 5 MAY 2015 372: 1887-1897
- 3 YEAR RESULTS OF PHASE 1-2 TRIAL
- IN HUMANS IMPROVEMENT IN RETINAL SENSITIVITY WERE MODEST AND FAILED TO PROTECT AGAINST ONGOING DEGERNERATION.
- GT LEAD TO TEMPORARY,VARIABLE AND INCOMPLETE RESTORATION OF RETINAL FUNCTION.
- UNMET DEMAND FOR RPE 65

# GENE THERAPY FOR LCA

- IN SUMMARY GENE THERAPY IS DIFFICULT BECAUSE OF THE MULTIPLE GENES INVOLVED.
- NO ADVERSE EFFECTS WITH LOWER DOSES.
- BEST AGE TO TREAT UNDETERMINED

# CONCLUSION

- IT IS MORE IMPORTANT TO KNOW THAT A PROBLEM EXISTS THAN WHAT DYSTROPY IS PRESENT

- DO NOT GIVE A DIAGNOSIS.DO NOT SPECULATE BEFORE ALL TEST RESULTS ARE IN AND SECOND OPINION FROM RETINA SPECIALIST OBTAINED

# CONCLUSIONS

- THE 4 TESTS THAT SHOULD BE DONE ON MOST DYSTROPHIES ARE:
  - ERG
  - EOG
  - VISUAL FIELD
  - OCT
- DARK ADAPTATION WHEN POSSIBLE

# CONCLUSION

- FAMILY HISTORY IS VERY IMPORTANT AND PARENTS SHOULD BE ENCOURAGED TO CALL RELATIVES

- RETINA SPECIALIST SHOULD GIVE DIAGNOSIS , DISCUSS STEPS IN GENE EVALUATION AND TREATMENT OPTIONS

# CONCLUSION

- WE ARE ABOUT TO ENTER A NEW AND EXCITING ERA IN DIAGNOSIS AND TREATMENT

- EVENTUALLY MOST DISEASES AND DYSTROPHIES WILL BE DEALT WITH AT THE GENETIC OR MOLECULAR LEVEL

# CASE HISTORY

- A 40 YEAR OLD MOTHER HAS AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA OCCURRING WHEN SHE WAS 24 YEARS OLD. SHE HAS A KNOWN MUTATION IN HER RHODOPSIN GENE. SHE BRINGS IN HER 5 YEAR OLD AND ASKS THAT THE CHILD BE TESTED TO SEE IF HE WILL GET THE DISEASE.

# CURRICULUM VITAE

NAME: Howard B. Cohen
MARITAL STATUS: Married
DOB: 7/16/39
CHILDREN: 5

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| HIGH SCHOOL: | Stuyvesant High School, New York City, N.Y.<br>Diploma - Academic | 1954-1961 |
| COLLEGE: | New York University, Heights, N.Y.<br>Degree: B.A. | 1957-1961 |
| MEDICAL SCHOOL: | New York Medical College<br>Degree: M.D. | 1961-1965 |
| INTERSHIP: | Jersey Shore Medical Center<br>Type: Rotating | 1965-1966 |
| ASSIGNMENTS: | General Medical Officer, 7th Special Forces Group, Fort Bragg, North Carolina | 1966-1967 |
| | General Medical and Surgical Officer, 5th Special Forces Group, Vietnam | 1967-1968 |
| | Chief, EENT, Fort Carson, Colorado | Mar 1972 - Sep 1974 |
| | Staff Ophthalmologist, Fitzsimons Army Medical Center, Denver, Colorado | Sep 1974 - Jul 1975 |
| | Asst Chief, Ophthalmology Service, Letterman Army Medical Center, Presidio of San Francisco, California | Feb 1977 - Feb 1983 |
| | Director, Vitreo-Retinal Service | Feb 1977 - Present |
| | Chief, Ophthalmology Service, Letterman Army Medical Center, Presidio of San Francisco, California | Feb 1983 - [redacted] 1987 |
| RESIDENCY: | Ophthalmology - Fitzsimons Army Medical Center, Denver, Colorado | Mar 1969 - Mar 1972 |
| FELLOWSHIPS: | Vitreo-Retinal Surgery - Dr. Charles Schepen Retina Associates, Fellow Retina Service, Massachusetts Eye and Ear Infirmary and Harvard Medical School | Aug 1975 - Feb 1977 |